

**ANTIMICROBIAL DRUGS ADVISORY COMMITTEE**

**CEFIDEROCOL BRIEFING DOCUMENT**

**NDA # 209445**

Advisory Committee Meeting

October 16, 2019



300 Campus Drive  
Florham Park, NJ 07932

**ADVISORY COMMITTEE BRIEFING MATERIALS:  
AVAILABLE FOR PUBLIC RELEASE**

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## LIST OF ABBREVIATIONS AND ACRONYMS

AE	Adverse event
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
APACHE II	Acute Physiology and Chronic Health Evaluation II
ARC	Augmented renal clearance
ARDS	Acute Respiratory Distress Syndrome
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUP	Acute uncomplicated pyelonephritis
AVI	Avibactam
BAL	Bronchoalveolar lavage
BAT	Best available therapy
BCRP	Breast cancer resistance protein
bid	Twice a day
BMI	Body-mass index
BSEP	Bile salt export pump
BSI	Blood stream infection
C <sub>0</sub>	Plasma concentration at the completion of dosing
CarbNS	Carbapenem nonsusceptible
CAZ	Ceftazidime
CD <sub>50</sub>	Convulsive dose required to achieve 50 % maximal effect
CEF	Ceftolozane
CEZ	Cefazolin sodium hydrate
CFDC	Cefiderocol
CFPM	Cefepime
CFU	Colony-forming units
CI	Confidence interval
cIAI	Complicated intra-abdominal infection
CL	Clearance
CLSI	Clinical and Laboratory Standards Institute
C <sub>max</sub>	Maximum plasma concentration
CNS	Central nervous system
COPD	Chronic Obstructive Pulmonary Disease
CPFX	Ciprofloxacin
CPIS	Clinical Pulmonary Infection Score
CR	Carbapenem resistant
CRE	Carbapenem-resistant Enterobacteriaceae
CrCl	Creatinine clearance
CRRT	Continuous renal replacement therapy
CS	Carbapenem susceptible

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CST	Colistin
cUTI	Complicated urinary tract infection
CV	Coefficient of variation
CVVH	Continuous venovenous hemofiltration
CVVHD	Continuous venovenous hemodialysis
CVVHDF	Continuous venovenous hemodiafiltration
CYP	Cytochrome P
DDI	Drug-Drug Interaction
ddQTcF	Time-matched and placebo- and baseline-adjusted QTcF
DSMB	Data and Safety Monitoring Board
Dx	Diagnosis
EA	Early assessment
ECG	Electrocardiogram/electrocardiography
ECMO	Extracorporeal membrane oxygenation
EEG	Electroencephalogram/electroencephalography
ELF	Epithelial lining fluid
EMA	European Medicines Agency
EOS	End of Study
EOT	End of treatment
ESBL	Extended spectrum $\beta$ -lactamase
ESCR	Extended-spectrum cephalosporin-resistant
ESRD	End-stage renal disease
EU	Europe
FDA	Food and Drug Administration
$fT_{>MIC}$	Fraction of time during the dosing interval where the free drug concentration in plasma exceeds the MIC
FU	Follow-up
GABA	Gamma-aminobutyric acid
GES	Guiana extended spectrum $\beta$ -lactamase
GN	Gram-negative
HAP	Hospital-acquired pneumonia
HCAP	Healthcare-associated pneumonia
HD	Hemodialysis
hERG	Human ether-à-go-go-related gene
HIV	Human immunodeficiency virus
IC <sub>50</sub>	Inhibitory concentration required to achieve 50 % maximal effect
ICH	International Council on Harmonisation
ICU	Intensive care unit
ICV	Intracerebroventricular
IMP	Imipenemase
INC	Increase from baseline
INR	International normalized ratio

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IPM	Imipenem
IPM/CS	Imipenem/cilastatin
ITT	Intent to Treat
IV	Intravenous
KPC	<i>Klebsiella pneumoniae</i> carbapenemase
LOS	Length of Stay
LTAC	Long-term acute care
MAD	Multiple Ascending Dose
MATE	Multidrug and toxin extrusion
MDR	Multidrug resistant
ME	Microbiologically evaluable
MEPM	Meropenem
MIC	Minimum inhibitory concentration
mITT	Microbiological intent to treat
MRI	Magnetic resonance imaging
MSSA	Methicillin-susceptible <i>S. aureus</i>
N/A	Not applicable
ND	Not done
NDA	New Drug Application
NDM	New Delhi metallo- $\beta$ -lactamase
NOAEL	No observed adverse effect level
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
OXA	Oxacillinase
PD	Pharmacodynamic
PER	<i>Pseudomonas</i> extended resistant enzyme
P-gp	P-glycoprotein
PI	Principal Investigator
PK	Pharmacokinetic
PT	Prothrombin time
PTA	Probability of target attainment
QD	Once daily
q6h	Every 6 hours
q8h	Every 8 hours
QTc	Corrected QT interval
QTcF	Corrected QT interval by Fredericia
RSE	Relative Standard Error
SAD	Single Ascending Dose
SAE	Serious adverse event
SD	Standard deviation
SE	Static Effect

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SNF	Skilled nursing facility
SOC	System Order Class
SOFA	Sequential Organ Failure Assessment
SSSI	Skin and skin structure infection
$t_{1/2,z}$	Terminal elimination half-life
TAZ	Tazobactam
tid	Three times daily
TOC	Test of cure
ULN	Upper limit of normal
US	United States
UTI	Urinary tract infection
V1	Volume of distribution in central compartment
V2	Volume of distribution in peripheral compartment
VAP	Ventilator-associated pneumonia
VIM	Verona integron-encoded metallo- $\beta$ -lactamase
VRE	Vancomycin-resistant enterococci
$V_z$	Volume of distribution during the terminal elimination phase
WHO	World Health Organization
XDR	Extensively drug resistant

## 1 EXECUTIVE OVERVIEW

Complicated urinary tract infections (cUTI) are the second leading cause of hospitalization in the elderly and have substantial morbidity and worse outcomes if the causative pathogens are carbapenem-resistant (CR) (Curns 2005, Zilberberg 2017).

Complicated UTIs are most frequently caused by *Escherichia coli* (65 %) and *Klebsiella pneumoniae* (8 %, Flores-Miereles 2015). Bloodstream infection (BSI) is often associated with cUTI, known as urosepsis, with an associated mortality rate of 9–31 % (Dreger 2015). The most frequent causes of urosepsis with CR organisms are *Pseudomonas aeruginosa* (44%), *K. pneumoniae* (22 %), *E. cloacae* (8%), *P. mirabilis* (8%) and *Stenotrophomonas maltophilia* (5%) (Shields 2019). Patients who develop cUTI due to a CR pathogen are at greater risk for prolonged hospital stays and progression to a BSI or urosepsis (Peach 2016, Zilberberg 2017).

Carbapenem resistance is a growing problem in the US and around the world, with increasing infections due to strains that are resistant to most or all currently available antibiotics. Compared to susceptible pathogens, CR pathogens cause prolonged hospital and intensive care unit (ICU) stays, worse discharge status, and greater mortality (Cai 2017b). The 3 leading pathogens on the World Health Organization's Priority Pathogen List are CR *P. aeruginosa*, CR *Acinetobacter baumannii*, and CR Enterobacteriaceae (CRE, WHO 2017). All of these have been isolated as causative pathogens of cUTI, with CR *P. aeruginosa*, CR *K. pneumoniae*, and *Stenotrophomonas maltophilia*, being the most common CR pathogens isolated in urine (Cai 2019). Carbapenem resistance was observed in 9,709 of 324,288 hospital urine tract isolates collected from 2010 to 2015 across 181 US hospitals (Cai 2019). In this survey of the CR pathogens causing cUTI, 47 % were *P. aeruginosa* and *K. pneumoniae* and *S. maltophilia* accounted for 19 % each.

Clinicians are in urgent need of novel therapeutic approaches to overcome the multiple resistance mechanisms that make these strains so difficult to treat. Recently, several new antibiotics have been introduced to address CRE infections, particularly the  $\beta$ -lactam/ $\beta$ -lactamase inhibitor combination drugs. These drugs have provided treatment options for some CR infections, but they do not address all resistant pathogens. As a result, last-resort antibiotics such as colistin, a drug developed decades ago but until recently rarely prescribed because of major renal and neurotoxicity, are used increasingly to manage CR infections. The emergence of colistin resistance in both *Enterobacteriaceae* and non-fermenters risks reducing the utility of this agent yet further.

**Cefiderocol** is the first antibiotic to overcome all 3 of the primary mechanisms (porin channel alterations,  $\beta$ -lactamase inactivation, and efflux pump overproduction) of Gram-negative bacterial resistance to  $\beta$ -lactams. Cefiderocol is a siderophore cephalosporin. As a siderophore it binds to ferric iron, an essential nutrient for bacterial growth and virulence, and is actively transported across the outer membrane common to all Gram-negative bacteria to enter the periplasmic space where it kills the bacteria by preventing cell wall synthesis. Other antibiotics cross the outer membrane via porin channels (cefiderocol can also cross via the porin channel), a less efficient method, and alterations in porins channels are a common cause of antibiotic resistance. Once in the periplasmic

space, cefiderocol is uniquely stable against all classes of  $\beta$ -lactamase enzymes, including the carbapenemase enzymes that are the predominant mechanism of  $\beta$ -lactam resistance in many bacterial species that cause UTIs. Finally, cefiderocol activity is not affected by efflux pumps, which actively remove many antibiotics from the bacteria. The unique siderophore structure of cefiderocol utilizes the bacteria's essential need for iron to enter and kill the cell, often described as a Trojan Horse strategy.

Multinational surveillance studies have shown that cefiderocol provides activity against more than 99 % of all Gram-negative clinical isolates, both Enterobacteriaceae (eg, *E. coli* and *K. pneumoniae*) and non-fermenters (eg, *P. aeruginosa*, *S. maltophilia*, and *A. baumannii*), including strains with little or no susceptibility to currently available therapies. The efficacy of cefiderocol against CR Gram-negative bacteria has been demonstrated in animal infection models involving the lung and thigh to establish a drug exposure profile ( $\% fT_{>MIC}$ ) that was used to establish an appropriate dose to treat infections in humans. This pharmacokinetic/pharmacodynamic (PK/PD) ratio was confirmed to be predictive of efficacy in animal infection models where the drug exposure over time was calibrated to match the PK profile in humans.

This potent non-clinical activity against carbapenem-resistant strains that cause life-threatening infections led the Food and Drug Administration (FDA) to grant cefiderocol a designation of qualified infectious disease product (QIDP) and Fast Track Designation. Discussions with the FDA resulted in agreement that the development pathway of cefiderocol could be a streamlined program focusing on a single, well-designed clinical trial in a site-specific infection where statistical comparison to a standard of care antibiotic medicine could be performed. This streamlined development approach enables approval of investigational antibiotics based on a single pivotal study conducted in a site-specific infection with robust support from microbiological and PK/PD assessments.

Shionogi chose to conduct a pivotal cUTI study using high-dose imipenem/cilastatin (IPM/CS) as a comparator for this purpose. This study was designed to enroll patients at risk for multi-drug resistant (MDR) infection, that is, those with complicated infections requiring hospitalization, who were mostly elderly and had multiple comorbidities. The cUTI trial was a double-blind, randomized, non-inferiority study in 448 hospitalized patients, of whom 300 received cefiderocol and 148 received IPM/CS. Patients with known IPM resistance were excluded. Patients were randomized to receive intravenous (IV) infusions over 1 hour of cefiderocol 2 g every 8 hours (q8h) or IPM/CS 1 g q8h for a recommended treatment duration of 7 to 14 days, with dose adjustment for reduced renal function, body weight, or both. The primary endpoint was a composite of microbiological eradication, defined as a post treatment urine culture that shows the bacterial uropathogen(s) found at a baseline of  $\geq 10^5$  colony-forming units (CFU)/mL is reduced to  $< 10^4$  CFU/mL, and clinical response, defined as resolution or improvement of baseline clinical signs and symptoms of cUTI, with no new symptoms of cUTI as assessed by the investigator.

The results of the study demonstrated non-inferiority according to the protocol-specified primary endpoint success criterion, and a post hoc analysis showed superiority to the

comparator. The difference in the primary composite endpoint at test of cure (TOC) was due to greater microbiologic eradication in the cefiderocol arm. The primary endpoint was achieved by 73 % of patients in the cefiderocol group and 55 % of patients in the IPM/CS group, with an adjusted treatment difference of 18.6 % (95 % confidence interval [CI]: 8.2, 28.9) in favor of cefiderocol. This result met the criterion for non-inferiority at the prespecified -15 % margin. The lower limit of 8.2 % is a robust effect of cefiderocol compared with IPM/CS.

Cefiderocol was effective both clinically and microbiologically in this population of patients with cUTI. The finding of non-inferiority with post-hoc superiority was consistent across subgroups.

Adverse event (AE) rates were similar in type and rate between treatment groups. Serious adverse event (SAE) rates were also similar in type and rate between groups. No difference in AE rates was observed in patients with increasing age or declining renal function. There was no case of Hy's law or drug-induced liver injury. Overall, the safety profile of cefiderocol appears to be consistent with the cephalosporin class, with no signal unique to cefiderocol.

These clinical, preclinical, and surveillance studies provide the safety and efficacy support for a limited use indication for cefiderocol under a streamlined development program. The proposed indication is **for the treatment of complicated urinary tract infections (cUTI), including pyelonephritis, caused by the following susceptible Gram-negative pathogens: *Escherichia coli* (including with concurrent bacteremia), *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Citrobacter freundii* complex, *Enterobacter cloacae* complex, *Morganella morganii*, and *Serratia marcescens*.** The "limited use" prescribing information will advise that cefiderocol should be used to treat infections where limited or no alternative treatment options are available and where cefiderocol is likely to be an appropriate treatment option, which may include use in patients with infections caused by documented or highly suspected CR and/or MDR Gram-negative pathogens.

The clinical dosing regimen of cefiderocol is 2 g administered every 8 hours by IV infusion over 3 hours. This regimen is based on extensive PK/PD analyses that supports the infusion time of 3 hours. Adjustments to the dose and/or frequency of administration are recommended for patients with renal impairment or augmented renal clearance (ARC, ie, enhanced renal function). The appropriateness of the recommended dosing regimen, including adjustments for renal function, has been validated through measuring the drug exposure in cefiderocol treated patients in all clinical studies.

This initial limited indication for cefiderocol in cUTI will be followed by subsequent applications for the treatment of nosocomial pneumonia based on the results of a recently completed clinical study named APEKS-NP (see [Section 11](#)).

The CREDIBLE-CR study investigated the efficacy and safety of cefiderocol versus best available therapy (BAT) in 150 patients with evidence of Gram-negative, carbapenem-

resistant pathogens. This open-label trial enrolled patients with nosocomial pneumonia, BSI/sepsis, or cUTI.

The CREDIBLE-CR study was not designed or powered to conduct hypothesis testing in order to compare treatment groups. The objectives were to provide descriptive statistics, and there were no prespecified hypotheses. Patient-level information was extensively collected in patient narratives and chronographs.

As this study was open-label, results have been shared with the FDA throughout the review of the application under discussion. Clinical and microbiological outcomes, which were primary response parameters of the study, were comparable between the 2 arms. The AE profile of cefiderocol and BAT were also comparable.

There was a difference in all-cause mortality in 18.0 %, 24.8 %, and 33.7 % of cefiderocol-treated patients and 12.2 %, 18.4 %, and 18.4 % of BAT-treated patients at Day 14, Day 28, and end of study (EOS), respectively.

None of the cefiderocol deaths was considered to be due to an adverse drug reaction by the investigator or Shionogi. The study data safety monitoring board (DSMB) reviewed the aggregate safety and efficacy information, as well the patient narrative information and at each scheduled DSMB meeting recommended the study continue without study protocol modification. Because the CREDIBLE-CR study was open label, an external, independent adjudication committee that was blinded to study treatment was convened after the study began to provide an independent assessment of the cause of death. This committee found that none of the deaths was likely due to an adverse reaction to study drug in either the cefiderocol or BAT treatment groups. The adjudication committee found that half of the patient deaths were the result of the patients' underlying medical co-morbidity or infection complications other than the original Gram-negative infection for which the patient was randomized into the study. However, the difference in mortality between cefiderocol-treated patients and BAT-treated patients was found in both infection-related deaths and non-infection-related deaths.

In addition to the above two studies, Shionogi conducted another study, APEKS-NP, which enrolled only patients with nosocomial pneumonia, either HAP, VAP or HCAP. This study was a double blinded, randomized non-inferiority study conducted globally comparing cefiderocol 2 g q8 h over 3 hours with meropenem 2 g q8 h over 3 hours. The non-inferiority margin was 12.5% for 14-day all-cause mortality as the primary endpoint. The 14-day all-cause mortality was 12.4 % versus 11.6 %; 28-day all-cause mortality was 21.2 % versus 20.1 %; EOS visit all-cause mortality was 26.9% versus 22.8%, for cefiderocol and meropenem, respectively in the microbiological intent-to-treat (mITT) population. A completed Clinical Study Report (CSR) has not been submitted to the FDA as part of the cUTI NDA under review, however, primary endpoint data from the completed study have been provided to the FDA and were publicly reported and presented in October 2019 ([Wunderink R et al, 2019](#)). Like the cUTI study, and unlike the CREDIBLE-CR study, the APEKS-NP study did not enrich for carbapenem non-susceptible or carbapenem resistant infections.

In addition to the clinical trials, Shionogi has provided cefiderocol upon unsolicited requests from attending physicians to treat patients with serious CR Gram-negative infections who have no other treatment options and could not be enrolled into a clinical trial. More than 200 requests for compassionate use have been received from around the world, demonstrating the unmet medical need.

Currently, Shionogi has confirmed information on 74 patients who have completed treatment in the compassionate use program. The FDA has supported Shionogi in fulfilling requests in the US. A tabular listing of patient information is available in [Appendix 15.8](#). Of the 74 completed cases, 49 survived their infection. Non-fermenting species were predominant, with *P. aeruginosa* the most frequent pathogen. All isolates were MDR or pan-resistant to current antimicrobials. Two cases have been published, one involving successful treatment of native aortic valve endocarditis caused by *P. aeruginosa* ([Edgeworth 2018](#)) and another patient with bacteremia pneumonia caused by XDR *Acinetobacter baumannii* and KPC producing *Klebsiella pneumoniae* ([Trecarichi 2019](#)). Additionally, 2 cases of *Achromobacter xylosoxidans* in lung transplant patients with cystic fibrosis will be presented at Infectious Disease Week in October ([Warner 2019](#)). The longest use of cefiderocol was for more than 90 days in a renal transplant patient who had *P. aeruginosa* infection of the intervertebral disc, with no apparent safety issues.

Throughout the development program, cefiderocol has demonstrated in vitro activity, in vivo animal efficacy, and human efficacy against Gram-negative MDR pathogens, including CR strains. The cUTI study was conducted in a population at risk of MDR infection, ie, they were older and more complicated than those in recent cUTI studies conducted to approve other antibiotics (Bass 2018). The proposed indication for cefiderocol is for limited use in cUTI, where few or no alternative treatment options are available. These will be patients with serious infections requiring hospitalization and for whom rapid, appropriate treatment is critical, whose cUTI is often superimposed on multiple comorbidities and may arise from serious underlying conditions. For these patients, the urgent medical need and the demonstrable benefits of cefiderocol outweigh the risks observed in clinical trials.

Appropriate antibiotic stewardship and resulting clinical supervision will ensure that cefiderocol will be used in patients with life-threatening infections who have limited treatment options.

## 2 INTRODUCTION

Cefiderocol has been developed to meet the pressing medical need for innovative new antibiotics that are effective against highly resistant Gram-negative infections. Cefiderocol is a siderophore cephalosporin whose unique mechanism of entry and stability against all classes of  $\beta$ -lactamases, including carbapenemases, enables it to overcome all three of the primary mechanisms of Gram-negative bacterial resistance to  $\beta$ -lactam antibiotics, including carbapenems (see [Section 4](#)).

Shionogi, the innovator and developer of cefiderocol, is an Osaka-based Japanese pharmaceutical company that has been discovering and developing anti-infectives and anti-virals since the 1950s. Some of the many antibiotics discovered and developed by Shionogi include sulfamethoxazole, ceftibuten, and doripenem.

The proposed indication for cefiderocol is for the **treatment of complicated urinary tract infections (cUTI), including pyelonephritis, caused by the following susceptible Gram-negative pathogens: *E. coli* (including with concurrent bacteremia), *K. pneumoniae*, *Proteus mirabilis*, *P. aeruginosa*, *Citrobacter freundii* complex, *Enterobacter cloacae* complex, *Morganella morganii*, and *Serratia marcescens*.**

As the development of cefiderocol has followed a streamlined development pathway and therefore has limited clinical safety and efficacy data, the prescribing information will advise that cefiderocol should be used to treat infections where limited or no alternative treatment options are available and where cefiderocol is likely to be an appropriate treatment option, which may include use in patients with infections caused by documented or highly suspected CR and/or MDR Gram-negative pathogens.

The clinical dosing regimen of cefiderocol is 2 g administered every 8 hours by IV infusion over 3 hours. This extended infusion time was demonstrated to optimize the pharmacodynamics and in vivo efficacy, although it should be noted that the same 2g/q8h dose (adjusted for renal impairment) was infused over 1 hour in the cUTI study. Adjustments to the dose and/or frequency of administration are recommended for patients with renal impairment or ARC (ie, enhanced renal function).

In agreement with the Food and Drug Administration (FDA), cefiderocol was developed in close accordance with the Guidance for Industry on the streamlined development of new antibiotics for the treatment of patients with life-threatening infections for whom few or no treatment options are available (FDA draft 2013, final 2017). The FDA Guidance recognized a streamlined development pathway for an approval with a limited use indication. Approval can be based on a single pivotal clinical trial and a smaller safety database in the treatment of patients with cUTI. Clinical trial evidence of safety and efficacy should be supplemented by robust data demonstrating in vitro microbiological efficacy, activity in appropriate animal models of infection, and a PK/PD relationship associated with efficacy in animal models that supports the clinical dose and frequency of administration.

The cefiderocol development program met and exceeded these recommendations.

Microbiological evidence of cefiderocol activity against resistant Gram-negative bacteria was demonstrated in four multinational surveillance studies using 30,459 randomly collected clinical isolates (see [Section 5](#)). In these studies, cefiderocol was highly active against over 99 % of Gram-negative aerobes, including CRE and CR strains of non-fermenters, such as *P. aeruginosa*, *A. baumannii*, and *S. maltophilia*.

Extensive animal studies, including the development of innovative animal models with human PK profiles, established the PK/PD parameters and the nonclinical efficacy and safety of cefiderocol (see [Sections 6](#) and [7](#)). This information was used to identify the dosing regimens employed in clinical studies and in the proposed labelling.

Six clinical pharmacology studies were conducted to support the proposed indication (see [Section 8](#)). These findings, along with those of a population PK analysis, further characterized the pharmacologic and safety profiles of cefiderocol and informed the dosing recommendations.

The clinical safety and efficacy of cefiderocol were demonstrated in the cUTI study, which enrolled 448 hospitalized patients with serious infections, median age above 65 years, many of whom had significant comorbidities (see [Section 9](#)). In this single pivotal trial, cefiderocol demonstrated noninferiority in the primary endpoint vs. the comparator IPM/CS; the findings of a post-hoc analysis were consistent with the superiority of cefiderocol. The efficacy of cefiderocol was consistent across all relevant subgroups, including age and severity of renal impairment. The safety of cefiderocol was comparable to that of IPM/CS, regarding rates of AEs and SAEs in both the cefiderocol-treated and patients treated with IPM/CS. The design of this study was aligned with that recommended in the FDA Guidance for cUTI studies (draft 2012, final 2015, revision 2018).

The marketing application being discussed is for the cUTI indication. Beyond this indication Shionogi has also conducted an open-label, real-world study of cefiderocol in seriously ill patients with CR Gram-negative infections (CREDIBLE-CR; see [Section 10](#)) and a comparative study of cefiderocol vs. meropenem in patients with nosocomial pneumonia caused by MDR Gram-negative infections (APEKS-NP; see [Section 11](#)). Both of these global studies were recently completed. Additionally, cefiderocol will be investigated in three pediatric studies and is being studied in an investigator-initiated clinical trial in adults with BSI.

Shionogi is also engaged in a compassionate use program that provides cefiderocol upon unsolicited request from attending physicians to patients with serious CR Gram-negative infections who have no other treatment options (see [Section 12](#) and [Appendix 15.8](#)).

The cefiderocol development program is appropriately focused on supporting the streamlined development and limited use indication for approval of an innovative treatment meeting an ongoing and increasingly urgent medical need.

### 3 MEDICAL NEED

The incidence of hospitalization and other serious sequelae due to cUTI is escalating, and MDR Gram-negative infections, in which carbapenem resistance is a critical challenge, are a major driver of this problem. Effective and safe treatment options for these highly resistant infections are limited at present.

#### 3.1 Complicated Urinary Tract Infections

Urinary tract infections account for the largest proportion (40 %) of all hospital-acquired infections in the US (Nicolle 2005). Whereas most UTIs are simple infections such as acute uncomplicated cystitis that affect young, otherwise healthy women, cUTIs are typically associated with structural or functional abnormalities or underlying conditions that increase the risk of infection and of treatment failure, such as stones, prostate hypertrophy/malignancy, urethral stricture, immunosuppression, or neurogenic conditions that impair bladder emptying. They are especially problematic where instrumentation, obstruction, foreign bodies, and scarring provide foci for persistent infection and the development of biofilms resistant to antibiotic penetration. Patients with these infections are often elderly, with multiple underlying comorbidities, including diabetes and dementia, and are taking multiple medications (Rowe 2013, Flores-Mireles 2015).

Recurrence of cUTI is common despite multiple courses of antibiotics with apparent activity. In fact, repeated courses of antibiotics drive the development of resistance among urinary tract pathogens.

Complicated UTIs are not limited to the bladder, often ascending to the kidney (pyelonephritis) and/or spreading to the bloodstream to cause bacteremia (urosepsis). Urosepsis is the most important sequelae of inappropriately treated cUTI. Complicated UTIs are the source of approximately 25 % of all adult sepsis cases and the most common cause of sepsis in older patients. They are responsible for up to 30 % of all severe sepsis or septic shock cases (Wagenlehner 2007), with an overall mortality rate of 25 % or higher (Ackermann 1996, Meyers 1989, Rosser 1999). Risk factors such as indwelling catheter, neutropenia, dementia, and functional dependence are associated with urosepsis and urosepsis-related mortality in cUTI patients (Peach 2016).

There are 2 to 3 million cases of cUTI annually in the USA, with over 400,000 cases being hospitalized (Flores-Mireles 2015, Simmering 2017). The past 15 years have seen a 50 % rise in the number of patients hospitalized with cUTI (Simmering 2017). Complicated UTIs are a leading cause of hospitalization in the elderly, second only to respiratory infections (Curns 2005)

The majority of cUTIs are caused by Gram-negative pathogens, such as *E. coli*, *P. aeruginosa*, and others (Flores-Mireles 2015). The 181-hospital Premier database provided information on over 500,000 Gram-negative infections; almost two-thirds of all isolates were from the urinary tract, and cUTIs were responsible for 29 % of the CR infections in the database (Cai 2017a). Overall, 6.7 % of Gram-negative isolates were CR; of these, almost 30 % of the urine isolates were CR, over 60 % were non-fermenters,

such as *P. aeruginosa*, *S. maltophilia*, and *A. baumannii*, whereas the Enterobacteriaceae comprised 40 % of CR cUTI.

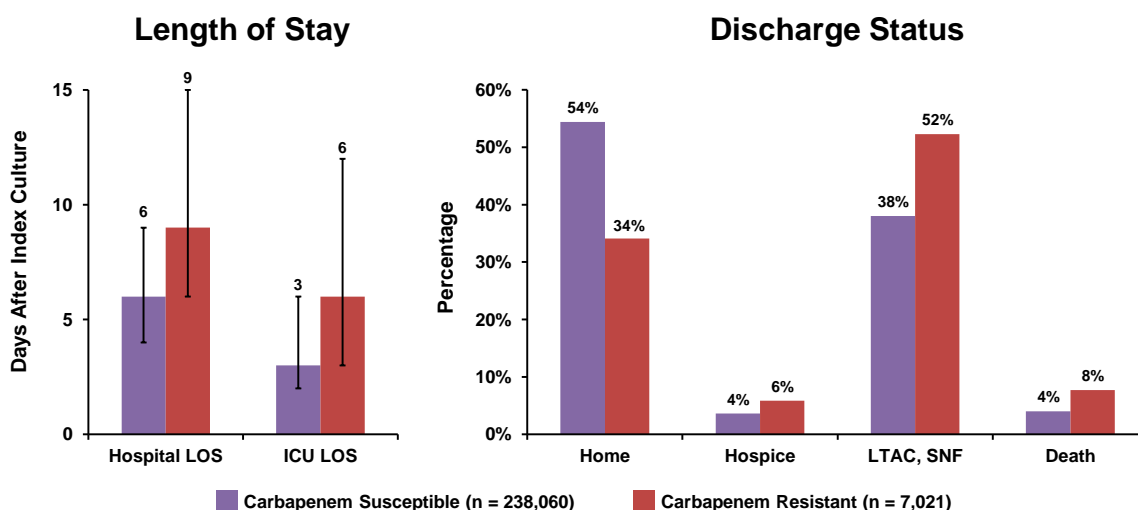
### 3.2 Carbapenem-Resistant cUTI

In 2017 the World Health Organization developed the Priority Pathogen List of bacterial species with resistance traits that urgently require new treatments ([WHO 2017](#)). The three top-priority critical pathogens with the most urgent need are CR *P. aeruginosa*, CR *A. baumannii*, and CR-ESBL producing Enterobacteriaceae.

Carbapenems are broad spectrum  $\beta$ -lactam antibiotics that were initially utilized as a second-line therapy or as the last resort to treat MDR, especially extended spectrum  $\beta$ -lactamase (ESBL)-producing pathogens. However, in the 2000s, resistance to first-line antibiotics increased, forcing a growing reliance on carbapenems. As a result, carbapenem resistance has emerged in the last decade. These infections are challenging to manage and cause substantial mortality and morbidity, particularly in healthcare-associated infections (Sievert 2013). The growing numbers of elderly, surgical, immunocompromised, and diabetic patients comprise an increasing population at risk for these infections.

Complicated UTI severity may increase significantly if the patient has multiple comorbidities and/or a CR pathogen. Several large-scale analyses have shown that objective outcomes such as length of hospital stay and mortality are markedly worse in patients infected with CR Gram-negative bacteria ([Chen 2019](#), [Liu 2015](#), [Schmier 2016](#), [Zilberberg 2016](#), [Zilberberg 2017](#)). Data collected from 2010 through 2015 identified 245,081 cUTI and showed that patients with CR cUTI had an average of 3-day longer stays in the hospital and the intensive care unit (ICU), compared with those with carbapenem-susceptible infections ([Figure 1](#), Premier Healthcare database). Patients with CR cUTI were less likely to be discharged home and more likely to be discharged to hospice or another long-term healthcare facility or die. Moreover, mortality rates among patients with CR cUTI were doubled, compared with patients with susceptible strains, 8 % vs. 4 %.

**Figure 1**                      **Impact of Carbapenem Resistance on Outcomes in cUTI**  
**(n = 245,081)**

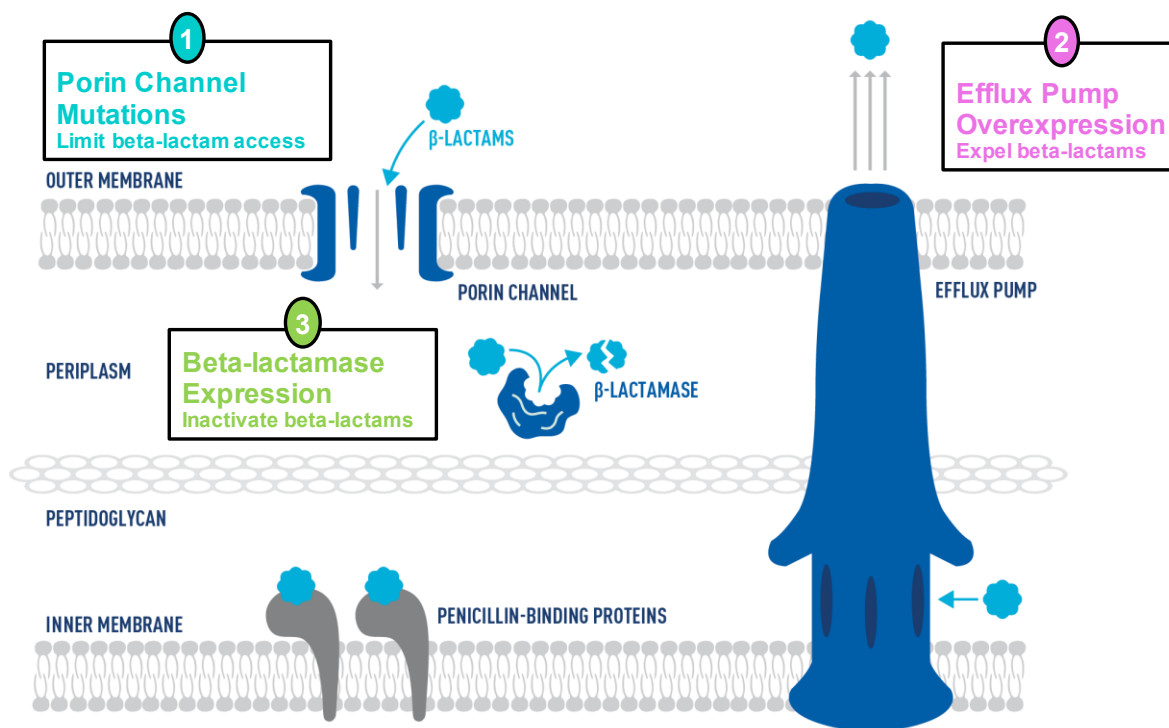


ICU, intensive care unit; LOS, length of stay; LTAC, long-term acute care; SNF, skilled nursing facility.

### 3.3 Mechanisms of Carbapenem Resistance

The three primary mechanisms of  $\beta$ -lactam resistance in Gram-negative bacteria are porin channel mutations, over-expression of efflux pumps, and  $\beta$ -lactamase enzymes (Figure 2). A porin channel allows passive diffusion of  $\beta$ -lactams across the bacterial outer membrane into the periplasm. The bacteria acquire resistance to antibiotics including carbapenems by reducing the number of porin channels expressed in the outer membrane or restricting the entry due to the porin channel mutation. Once the antibiotic crosses into the periplasmic space, the bacteria can expel the drug through the efflux pumps. The bacteria acquire resistance to antibiotics, including carbapenems, due to an increased expression of efflux pumps. Antibiotics that cross into the periplasmic space and are not expelled by efflux pumps may be subject to enzymatic degradation by  $\beta$ -lactamases, the most common type of  $\beta$ -lactam resistance. Multiple resistance mechanisms may co-exist in a given pathogen.

**Figure 2                       $\beta$ -Lactam Resistance Mechanisms**



Carbapenem resistance may occur with or without carbapenemase production. Four classes of  $\beta$ -lactamases are recognized, and carbapenemases are observed in three classes. Class B, the metallo- $\beta$ -lactamases, including New Delhi metallo- $\beta$ -lactamase (NDM 1-20), Verona integron-encoded metallo- $\beta$ -lactamase (VIM 1-46), imipenemase (IMP 1-53), and L-1 in *S. maltophilia*, are the most challenging from a clinical perspective. Classes A and D are serine  $\beta$ -lactamases. Class A includes *K. pneumoniae* carbapenemases (KPCs), Guiana extended spectrum (GES) carbapenemases, while class D includes oxacillinase (OXA) enzymes with the clinically relevant carbapenemases such as OXA-23, OXA-24, OXA-48 and OXA-58 carbapenemases. Class C  $\beta$ -lactamases, AmpC, are not considered carbapenemases, but when they occur in conjunction with porin channel closure and over-expression of efflux pumps, they confer carbapenem resistance.

### 3.4 Recent Antibiotic Development

Recent antibiotic drug development has been a constant struggle against evolving and increasingly resistant Gram-negative bacteria. A timeline of notable milestones in recent Gram-negative antibiotic history is provided in [Table 1](#).

**Table 1 History of Antibiotics for Resistant Gram-Negative Pathogens**

<b>1960s</b>	<b>• Polymyxins approved</b>
<b>1970s</b>	<b>• Polymyxins “shelved” due to nephrotoxicity and neurotoxicity issues</b>
<b>1980s</b>	<b>• Aminoglycosides introduced but have toxicity risks</b>
<b>1980s</b>	<b>• Third generation cephalosporins, fluoroquinolones, and carbapenems approved</b>
<b>1980s/ 1990s</b>	<b>• Resistance to third generation cephalosporins and fluoroquinolones emerged, resulting in increased carbapenem use</b>
<b>2000s</b>	<b>• Carbapenem resistance emerged among Enterobacteriaceae</b>
<b>2010s</b>	<b>• Polymyxins returned due to lack of options, despite toxicity • Resistance emerging</b>

In response to global concerns regarding this unmet medical need, and the FDA Guidance on streamlined development ([FDA 2017](#)), several new antibiotics have been developed and approved in the US, many of which have activity against certain types of Gram-negative resistant pathogens. These new drugs include Zerbaxa<sup>®</sup> (ceftolozane and tazobactam), Avycaz<sup>®</sup> (ceftazidime and avibactam), Vabomere<sup>™</sup> (meropenem and vaborbactam), Zemdri<sup>™</sup> (plazomicin), Xerava<sup>™</sup> (eravacycline), and Recarbrio<sup>™</sup> (imipenem, cilastatin, and relebactam). Development and approval of these drugs has been an important achievement in the field of antibiotics at this critical time; however, none of the newer therapies is effective against all mechanisms of resistance described above. Most lack reliable activity against pathogens that over-express efflux pumps or have porin channel mutations, and none of the  $\beta$ -lactam/ $\beta$ -lactamase inhibitor combination drugs has activity against metallo-carbapenemases, a resistance mechanism that is spreading worldwide. Zerbaxa also is inactive against bacteria that produce serine-carbapenemases, such as KPC or OXA-48 ([Kaye 2018](#)). As a result, clinicians increasingly are turning again to the polymyxins, both colistin and polymyxin B, despite their toxicity and the recent appearance of plasmid-borne resistance.

### 3.5 Medical Need Conclusions

Clinicians are increasingly challenged by the difficulty of prescribing appropriate empiric therapy for cUTI, in a patient who may have Gram-negative MDR and CR pathogens, such as *K. pneumoniae*, *P. aeruginosa*, *A. baumannii*, and *S. maltophilia*, which are not consistently susceptible to available agents, including those recently approved. Gram-negative pathogens are the major cause of cUTI, which in the US affects 2-3 million individuals annually, of whom 400,000 will be hospitalized ([Flores-Mireles 2015](#)). Affected patients will invariably have underlying comorbidities such as diabetes, structural issues such as blockages, stones, or biofilms, and/or host defense deficiencies. These underlying factors, in addition to CR pathogens, pose a major clinical challenge.

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New treatment options are needed to overcome all three primary mechanisms of resistance to  $\beta$ -lactam antibiotics. They must cover ESBLs and both serine and metallo-carbapenemases and thereby demonstrate efficacy against CRE and CR non-fermenters, with a manageable safety profile. The enhanced ability to penetrate and remain in the cell to kill the bacterium is a further requirement in the fight against MDR and CR infections.

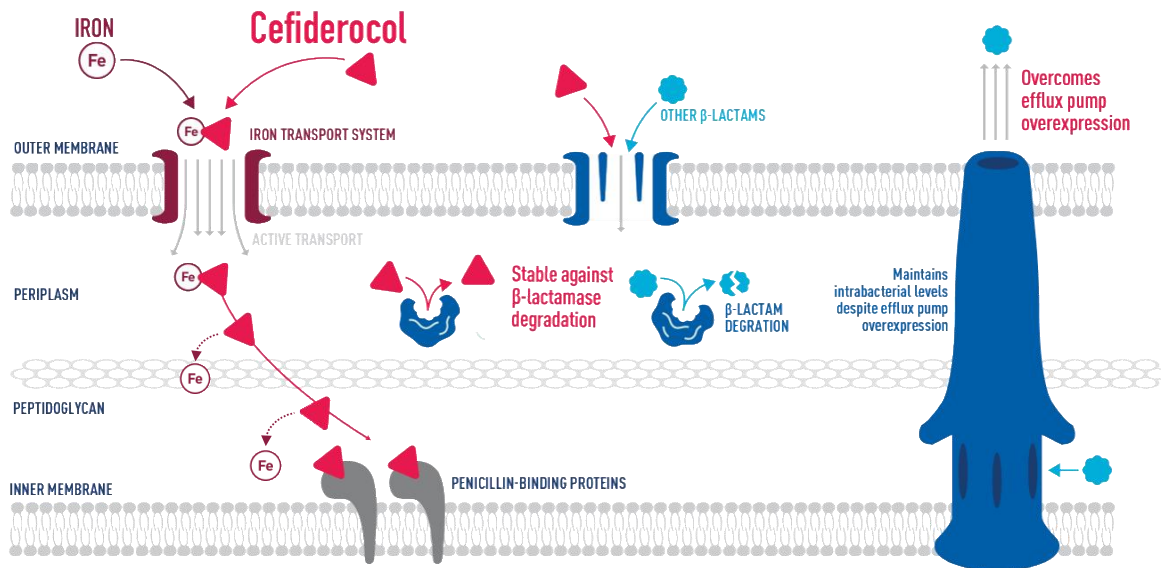
Compared to susceptible strains, CR pathogens cause increased hospital and ICU stays, worse discharge status, and increased mortality. With few reliable options, clinicians are turning to a large range of combinations that often include old drugs with significant toxicity, such as colistin.

The clinical impact of CR cUTI, including life-threatening complications such as urosepsis when the infection is not adequately treated, is significant and likely increasing as the population ages and antibiotic resistance escalates. New efficacious and safe therapies are urgently needed.

## 4 CEFIDEROCOL MECHANISM OF ACTION

The structure and mechanism of action of cefiderocol are unique in that it addresses all three of the primary mechanisms of  $\beta$ -lactam resistance in Gram-negative bacteria (Figure 3).

**Figure 3 Cefiderocol Overcomes 3 Mechanisms of  $\beta$ -Lactam Resistance**

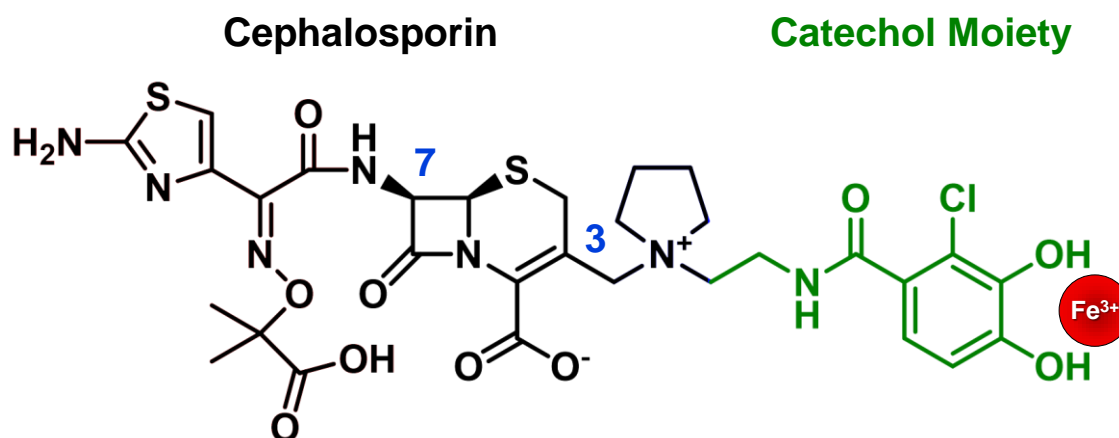


Cefiderocol is a single molecule consisting of a cephalosporin antibiotic to which a catechol moiety is linked that can bind to a single iron atom. Cefiderocol functions as a siderophore, which is a molecule that bacteria deploy to obtain iron from the extracellular environment. Most antibiotics enter Gram-negative pathogens by passive diffusion through porin channels. As described in [Section 3](#) above, porin channel mutations are one of the key mechanisms of resistance to  $\beta$ -lactam antibiotics. As a siderophore cephalosporin, cefiderocol overcomes the porin channel mechanism of resistance that blocks antibiotic entry into the cell by using the iron transport function of the cell to gain entry, although cefiderocol can also enter the cell through porin channels. Cefiderocol, being a poor substrate for these efflux pumps e.g. Mex, Acr, retains its activity against antibiotic resistant Gram-negative pathogens that express higher numbers of efflux pumps, a resistance mechanism that rapidly removes other antibiotics from the periplasmic space. Inside the periplasmic space, cefiderocol acts as a  $\beta$ -lactam, killing the bacteria by inhibiting cell wall synthesis as is the case for all cephalosporins. Its side chains provide both steric and ionic properties, which enable cefiderocol to withstand bacterial enzymes ( $\beta$ -lactamases) that break down other  $\beta$ -lactam antibiotics, and thus it is stable against all classes of  $\beta$ -lactamases, including carbapenemases. The ability of cefiderocol to overcome all three mechanisms of  $\beta$ -lactam resistance translates clinically to low MICs for nearly all Gram-negative pathogens. Less than 1 % of clinical isolates were non-susceptible to cefiderocol due to multiple factors including some specific  $\beta$ -lactamases.

As a siderophore cephalosporin, cefiderocol exhibits a “Trojan Horse” approach in its ability to bind extracellular free iron and be transported across the outer membrane. Iron is an essential nutrient for bacterial pathogen survival. During a bacterial infection, the host immune system releases various acute-phase proteins such as lactoferrin to sequester host iron in an attempt to inhibit bacterial growth. Starved of iron, the Gram-negative pathogen increases its secretion of siderophores, which bind host iron with high affinity. The siderophore-iron complex is then recognized by siderophore-iron transporters, which actively transport the complex across the bacterial cell membrane into the periplasmic space. The “Trojan Horse” metaphor applies because the bacteria “think” they are bringing into the cell something beneficial (iron), when in fact they are bringing in something that will kill it (a cephalosporin).

The third and most important  $\beta$ -lactam resistance mechanism in Gram-negative pathogens is the expression of  $\beta$ -lactamases—including carbapenemases—that inactivate the antibiotic by degradation. The chlorocatechol and pyrrolidinium group on the C-3 side chain and a carboxypropanoxyimino group on the C-7 side chain of the cefiderocol molecule (Figure 4) likely confer stability against inactivation by all classes of  $\beta$ -lactamases, enabling it to retain activity against Gram-negative pathogens expressing serine carbapenemases and metallo-carbapenemases. There is a significant unmet need for antibiotics that are resistant to degradation by these enzymes.

### Figure 4 Cefiderocol is a Siderophore Cephalosporin



## 5 MICROBIOLOGY AND SURVEILLANCE

Cefiderocol has demonstrated stability against inactivation by members of all classes of  $\beta$ -lactamases and retains activity against Gram-negative pathogens expressing serine carbapenemases, such as KPC, OXA-48, OXA-23, OXA-40, and OXA-58, as well as pathogens expressing metallo-carbapenemases, such as NDM, VIM, IMP, and L1, where there is a significant unmet need for antibiotics that are resistant to degradation by these enzymes. In addition, cefiderocol has been shown to be stable against AmpC and shown activity against AmpC-producers.

### 5.1 Susceptibility Analyses from Surveillance Studies

To determine susceptibility of Gram-negative bacteria to cefiderocol, multinational surveillance studies were conducted over three consecutive years (2014 to 2017) using systematically collected clinical isolates from approximately 100 clinical laboratories in North American and European countries. A separate multinational surveillance study of Proteaceae clinical isolates was also conducted. The antibacterial activity of cefiderocol was determined in iron-depleted cation-adjusted Mueller-Hinton medium (ID-CAMHB), a method approved by the Clinical and Laboratory Standards Institute (CLSI). Standard media has excess iron relative to the human host and we have demonstrated better correlation between the in vivo therapeutic efficacy and the in vitro antibacterial activity in ID-CAMHB iron deficient media.

A 4  $\mu\text{g/mL}$  concentration of cefiderocol is readily achieved in plasma and CLSI has recognized this as a provisional breakpoint for susceptibility testing for both Enterobacteriaceae and non-fermenters.

Importantly, multinational surveillance studies included comparator agents, including the newly available  $\beta$ -lactam/ $\beta$ -lactamase inhibitor combinations (ceftazidime/avibactam and ceftolozane/tazobactam) as well as ciprofloxacin and colistin. Only cefiderocol provides reliable ( $> 90\%$ ) activity against all organisms isolated from North America and Europe (Table 2). Of the approximately 30,000 isolates in the surveillance studies, 161 isolates had a cefiderocol MIC  $> 4\ \mu\text{g/mL}$ . Among these, 128 isolates were *A. baumannii* and 87 isolates were from Russia. Note that 70 isolates among the 161 had an MIC of 8  $\mu\text{g/mL}$ . Of the US isolates, cefiderocol was shown to be 99.7% active against all the Gram-negative isolates at an MIC of  $\leq 4\ \mu\text{g/mL}$ . Among the US isolates (Table 3), 19 of 11,168 had a cefiderocol MIC  $> 4\ \mu\text{g/mL}$ . These included 9 *A. baumannii*, 6 Enterobacteriaceae, 3 *B. cepacia* complex, and 1 *P. aeruginosa*.

Another global surveillance study of 1873 carbapenem non-susceptible clinical isolates from 52 countries found that 97 % of carbapenem non-susceptible Enterobacteriaceae (1021 strains) and 95.8 % of carbapenem non-susceptible non-fermenter strains (828 strains), including *P. aeruginosa*, *A. baumannii*, and *S. maltophilia*, were susceptible to cefiderocol at  $\leq 4\ \mu\text{g/mL}$  (Table 4).

Among 29,960 randomly collected Gram-negative strains (both carbapenem non-susceptible [CarbNS] and carbapenem susceptible [CS]) of Enterobacteriaceae,

*P. aeruginosa*, *A. baumannii*, and *S. maltophilia*, 99.6 % were susceptible to cefiderocol at a MIC of  $\leq 4$   $\mu\text{g/mL}$  (Figure 5). The susceptibility profiles of cefiderocol against the US isolates were similar to isolates from other countries.

In the subset of carbapenem non-susceptible strains (N = 4,862), 97.7 % were susceptible to cefiderocol at an MIC of  $\leq 4$   $\mu\text{g/mL}$  (Figure 6).

**Table 2**                      **Summary of the Ratio (%) of Susceptibility Strains of Cefiderocol in 4 Multinational Surveillance Studies (SIDERO-WT) Using All the Tested Clinical Strains**

Species (Strains, n)	Ratio (%) of Susceptible Strains				
	CFDC	CAZ/ AVI	CEF/ TAZ	CPFX	CST
All Gram-negative (30459)	99.5	90.2	84.3	72.9	95.5
Enterobacteriaceae (20949)	99.9	99.2	91.4	80.6	96.5
Non-fermenters (9510)	98.5	70.3	68.5	55.9	93.7
CarbNS Enterobacteriaceae <sup>c</sup> (654)	98.2	77.7	8.4	13.9	75.6
CarbNS non-fermenters (4331)	97.6	41.0	34.6	21.2	86.9
CarbNS <i>P. aeruginosa</i> (1154)	99.9	75.4	76.1	38.7	98.4
CarbNS <i>A. baumannii</i> (1891)	94.9	16.2	7.8	0.5	85.1
<i>S. maltophilia</i> (1173)	99.8	42.9	34.3	34.5	78.2

AVI, avibactam; CarbNS, carbapenem nonsusceptible; CAZ, ceftazidime; CEF, ceftolozane; CFDC, cefiderocol; CPFX, ciprofloxacin; CFPM, cefepime; CST, colistin; ESCR, extended-spectrum cephalosporin-resistant; MEPM, meropenem; MIC, minimum inhibitory concentration; TAZ, tazobactam.

Ratios (%) of susceptible strains were calculated by using the following MIC criteria:

Cefiderocol MIC  $\leq 4$   $\mu\text{g/mL}$ , CAZ/AVI MIC  $\leq 8$   $\mu\text{g/mL}$ , CEF/TAZ MIC  $\leq 2$   $\mu\text{g/mL}$  for

Enterobacteriaceae,  $\leq 4$   $\mu\text{g/mL}$  for non-fermenters, CPFX MIC  $\leq 1$   $\mu\text{g/mL}$ , CST MIC  $\leq 2$   $\mu\text{g/mL}$ .

*Burkholderia* spp. and *Serratia* spp. were not included as CST-resistant strains

**Table 3 Summary of Ratio (%) of Susceptibility Strains of Cefiderocol Surveillance Studies (SIDERO-WT) of Clinical Strains isolated from the US**

Species (Number of Strains)	Ratio (%) of Susceptible Strains				
	CFDC	CAZ/AVI	CEF/TAZ	CPFX	CST
All Gram-negative (11168)	99.7	93.1	89.3	77.6	96.8
Enterobacteriaceae (7840)	99.9	99.9	94.3	84.2	97.3
Non-fermenters (3328)	99.2	77.2	77.6	62.3	95.7
CarbNS Enterobacteriaceae (127)	100	96.1	18.9	29.9	92.6
CarbNS non-fermenters (1279)	98.1	49.6	45.3	24.9	89.4
CarbNS <i>P. aeruginosa</i> (369)	100	89.4	92.4	39.6	99.7
CarbNS <i>A. baumannii</i> (448)	95.3	19.4	14.5	0.7	91.3
<i>S. maltophilia</i> (422)	99.8	43.1	34.4	34.6	78.4

Ratios (%) of susceptible strains were calculated by using the following MIC criteria:  
Cefiderocol MIC  $\leq 4$   $\mu\text{g/mL}$ , CAZ/AVI MIC  $\leq 8$   $\mu\text{g/mL}$ , CEF/TAZ MIC  $\leq 2$   $\mu\text{g/mL}$  for Enterobacteriaceae,  $\leq 4$   $\mu\text{g/mL}$  for non-fermenters, CPFX MIC  $\leq 1$   $\mu\text{g/mL}$ , CST MIC  $\leq 2$   $\mu\text{g/mL}$ .

*Burkholderia* spp. and *Serratia* spp. were not included as CST-resistant strains

US isolates are a subset of the multinational isolates presented in [Table 2](#)

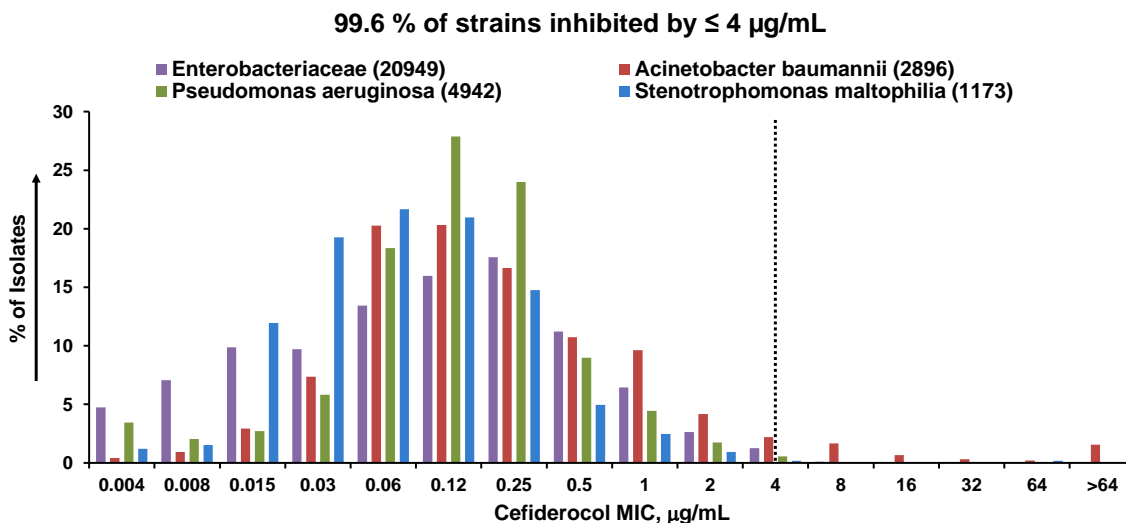
**Table 4 Susceptibility of CRE and MDR Non-Fermenters A Global Study (SIDERO CR-2014/2016)**

Species (Strains, n)	Ratio (%) of Susceptible Strains				
	CFDC	CAZ/AVI	CEF/TAZ	CPFX	CST
All Gram-negatives (1873)	96.2	57.4	9.6	8.2	84.6
CarbNS Enterobacteriaceae (1021)	97.0	77.0	1.6	11.4	80.9
CarbNS non-fermenters (828)	95.8	32.7	18.0	4.0	88.8
CarbNS <i>P. aeruginosa</i> (252)	99.2	33.7	22.2	0.8	99.6
CarbNS <i>A. baumannii</i> (361)	90.9	18.0	3.6	0	94.5
<i>S. maltophilia</i> (218)	100	56.9	37.6	14.7	67.0

Ratios (%) of susceptible strains were calculated by using the following MIC criteria:  
Cefiderocol MIC  $\leq 4$   $\mu\text{g/mL}$ , CAZ/AVI MIC  $\leq 8$   $\mu\text{g/mL}$ , CEF/TAZ MIC  $\leq 2$   $\mu\text{g/mL}$  for Enterobacteriaceae,  $\leq 4$   $\mu\text{g/mL}$  for non-fermenters, CPFX MIC  $\leq 1$   $\mu\text{g/mL}$ , CST MIC  $\leq 2$   $\mu\text{g/mL}$ .

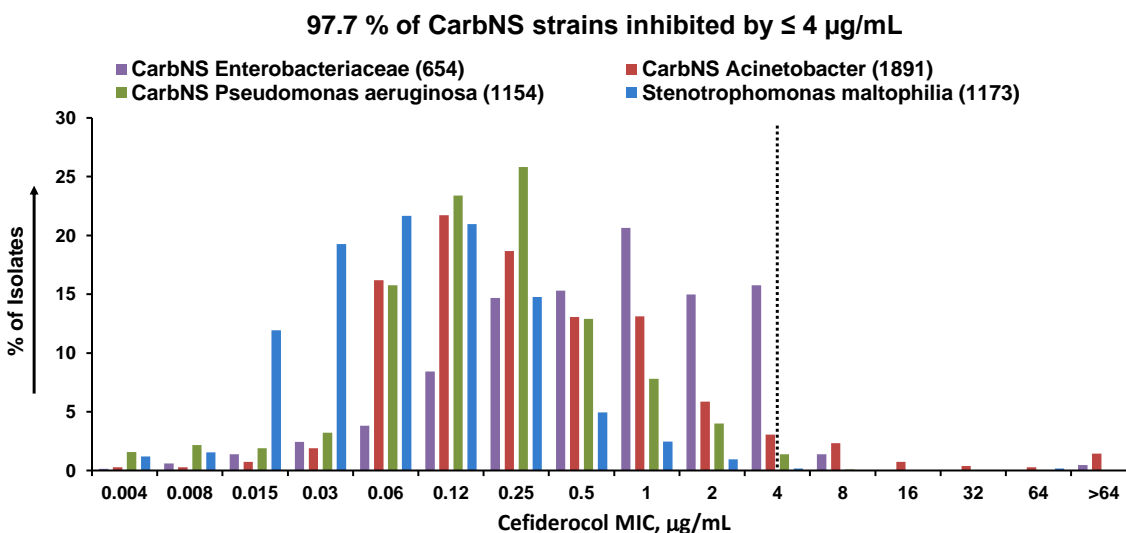
*Burkholderia* spp. and *Serratia* spp. were not included as CST-resistant strains

**Figure 5 Cefiderocol MIC Distribution of 29,960 Gram-Negative Multi-national Clinical Isolates (SIDERO-WT 2014–2016 Carbapenem Susceptible and Carbapenem Non-susceptible Strains)**



MIC, minimum inhibitory concentration.  
Number of strains are in parentheses.

**Figure 6 Cefiderocol MIC Distribution of 4,862 Carbapenem Nonsusceptible Multi-national Clinical Isolates (SIDERO-WT 2014–2016)**

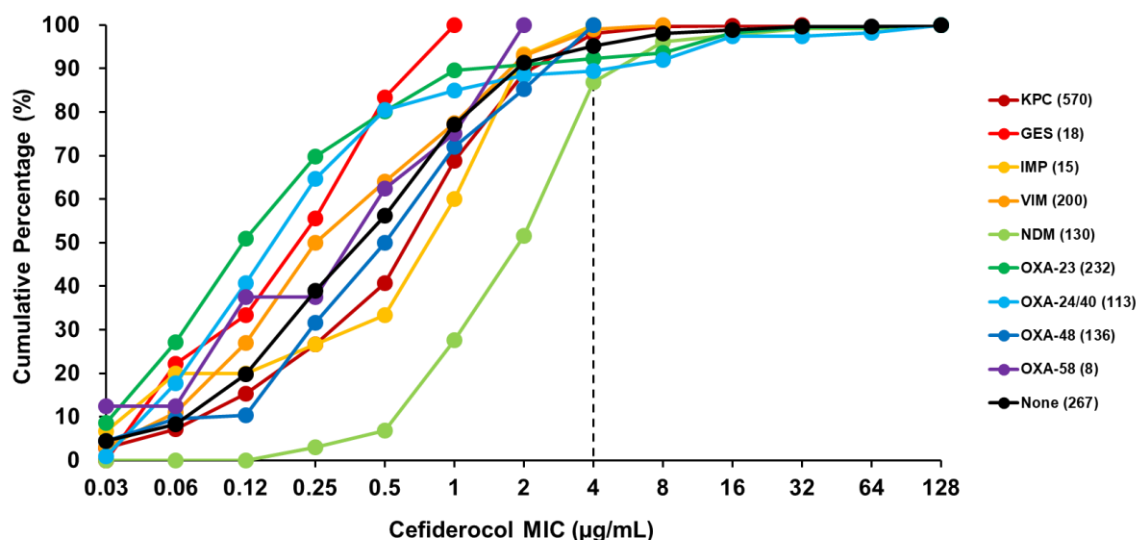


CarbNS, carbapenem nonsusceptible; MIC, minimum inhibitory concentration.  
Number of strains are in parentheses.

## 5.2 Molecular Analysis of Carbapenem Resistance-Related Genes

A molecular analysis of carbapenem resistance-related genes was conducted using CarbNS isolates from 2 multinational surveillance studies, SIDERO-WT-2014 and SIDERO-CR. Specific carbapenemase enzymes were identified in each strain. Based on the molecular analysis, cefiderocol has potent activity against carbapenemase-producers GES, KPC, VIM, NDM, IMP, and OXA-23, OXA-24/40, and OXA-58. A similar cefiderocol MIC distribution is seen regardless of the type of specific carbapenemase enzymes produced by the isolates (Figure 7) although the MICs for NDM containing isolates is shifted to the right indicating less activity.

**Figure 7** Cefiderocol MIC Distribution by Enzyme Type in Carbapenem Nonsusceptible Clinical Isolates (2014 SIDERO-WT, SIDERO-CR Studies)



GES, Guiana extended spectrum; KPC, *Klebsiella pneumoniae* carbapenemase; IMP, imipenemase; OXA, oxacillinase; MIC, minimum inhibitory concentration; NDM, New Delhi metallo- $\beta$ -lactamase; VIM, Verona integron-encoded metallo- $\beta$ -lactamase.

## 5.3 Investigations of the Potential Development of Resistance

Shionogi has assessed the cefiderocol resistance mechanism using the cefiderocol high MIC isolates from multi-national surveillance studies and the non-clinical resistance development studies.

The cefiderocol high MIC isolates from SIDERO WT surveillance studies were due to the production of multiple  $\beta$ -lactamases occurring simultaneously in the same pathogen; PER producing *A. baumannii* (mainly from Russia and Turkey) and NDM producing Enterobacteriaceae were also observed. However, most other PER or NDM producers

showed susceptibility to cefiderocol, suggesting that even with the presence of PER or NDM in pathogens with high MICs, there may be additional factors contributing to cefiderocol resistance. The addition of avibactam to cefiderocol reduces the MICs of *A. baumannii* containing PER, and the addition of both avibactam and NDM inhibitors reduced the activity of cefiderocol against NDM containing Enterobacteriaceae.

A low propensity for the development of resistance to cefiderocol is indicated by the low frequency of resistance from large inocula and extensive serial passage studies, including CR strains. Knock-out experiments deleting specific iron transport genes caused small MIC increases of cefiderocol, but they were still susceptible based on the provisional breakpoint. Following serial passage and in vitro pharmacodynamic modelling using human exposures, no signs of resistance emerged (Kohira 2018). A study of “adaptive” resistance was not observed with cefiderocol (Ghazi 2018). Adaptive resistance is an observation of the poor relationship between *in vitro* activity and *in vivo* efficacy described with the use of 2 hydroxyperidone siderophore monobactams that are no longer being developed. Finally, an in vivo efficacy study with cefiderocol treatment for 3 days using murine thigh infection models showed that resistance acquisition was observed infrequently; less than 1%.

## 5.4 Microbiology and Surveillance Conclusions

Cefiderocol inhibits almost all Gram-negative aerobic pathogens, including difficult to treat CR bacteria, both Enterobacteriaceae and non-fermenters. Unlike other cephalosporins, cefiderocol has limited activity against Gram-positive and anaerobic bacteria. Additional antibiotics with Gram-positive or anaerobic activity are needed for mixed infections needing Gram-positive or anaerobic activity.

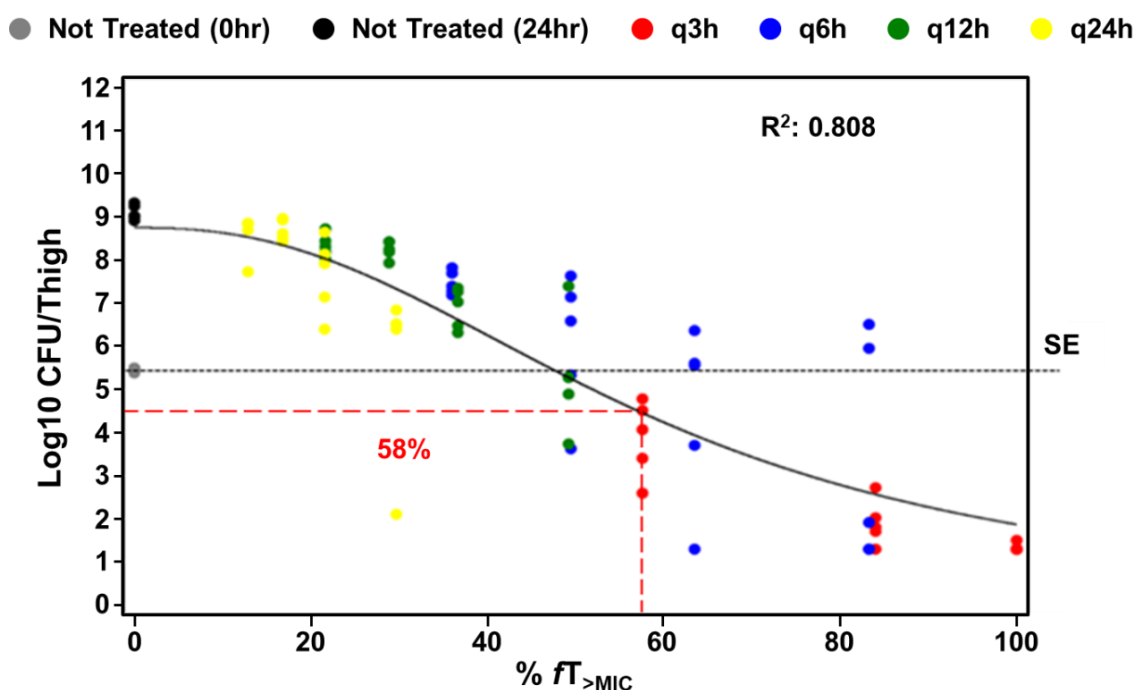
Based on the surveillance studies, more than 99 % of all Gram-negative pathogens and more than 98 % of CarbNS pathogens are susceptible to cefiderocol at an MIC of equal to or less than 4 µg/mL. The susceptibility to cefiderocol is not affected by β-lactamase enzymes, porin changes, or efflux over-expression. Gram-negative pathogens, including CR strains, show a low propensity for the development of resistance to cefiderocol.

## 6 NONCLINICAL EFFICACY AND PHARMACOKINETIC/ PHARMACODYNAMIC ASSESSMENTS

### 6.1 PK/PD Parameter for Therapeutic Efficacy

The PK/PD parameter for cefiderocol is %  $fT_{>MIC}$  as expected for a beta-lactam (cephalosporin) antibiotic. In a standard dose fractionation study in a neutropenic murine thigh using a strain of *P. aeruginosa*, the %  $fT_{>MIC}$  was the best measure of the in vivo efficacy of cefiderocol, and a bactericidal effect (1 log reduction) was observed at 58 % of %  $fT_{>MIC}$ , similar to other cephalosporins. (Figure 8).

**Figure 8** Dose Fractionation Study in Murine Thigh Model of *P. aeruginosa* Infection With %  $fT_{>MIC}$  as Pharmacokinetic/Pharmacodynamic Index for Cefiderocol



CFU, colony forming unit;  $fT_{>MIC}$ , fraction of time during the dosing interval where the free drug concentration exceeds the MIC (0.25 µg/mL); MIC, minimum inhibitory concentration; SE, static effect. The red line equals 1 log drop = 57.6; a 2-log drop is 69.7.

Subsequently, a series of dose response studies were conducted using standard neutropenic murine thigh models of infection by both Enterobacteriaceae (*E. coli*, *K. pneumoniae*) and *P. aeruginosa*, including CR isolates with specific carbapenem resistance genes such as KPC, NDM, and IMP.

In addition, a series of dose response studies were also conducted using neutropenic murine lung models of infection by both Enterobacteriaceae (*E. coli*, *K. pneumoniae*) and non-fermenters (*P. aeruginosa*, *A. baumannii*, and *S. maltophilia*).

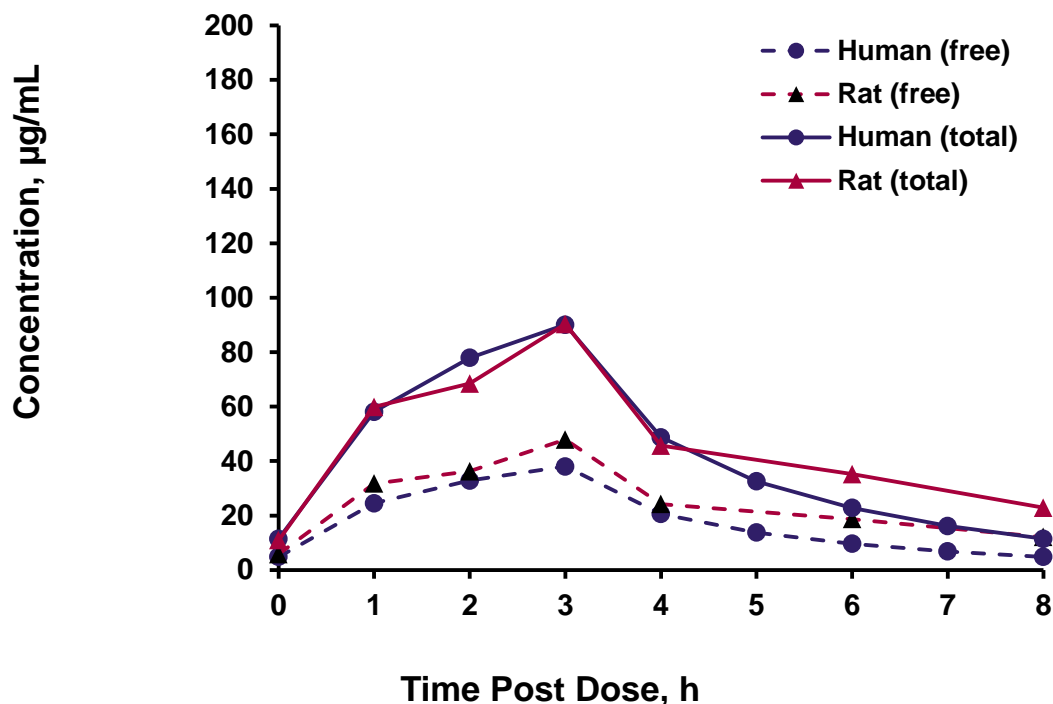
The calculated %  $fT_{>MIC}$  value of cefiderocol required for a static or cidal effect (reduction to the number of viable bacterial cells at the infection site) ranges fairly widely among individual test isolates, but there was no difference on the mean %  $fT_{>MIC}$  value required for efficacy for Enterobacteriaceae and *P. aeruginosa* between 2 different sites of infection.

The results of these neutropenic mouse thigh infection models, which are a standard methodology for PK/PD analysis, established the bactericidal value (1 log reduction) of the 75 %  $fT_{>MIC}$  value for the selection of the cefiderocol human dose. This value of 75 %  $fT_{>MIC}$  was determined as the average value from multiple isolates including carbapenem-resistant isolates from the dose ranging study using mouse thigh infection models (See [Appendix 15.1](#)), which was considered a conservative value compared with the established 58 %  $fT_{>MIC}$  obtained from the dose fractionation study. To confirm the 75 %  $fT_{>MIC}$  PTA selected from the dose response studies, an additional evaluation using mouse thigh infection models with multiple isolates of multiple bacterial species such as Enterobacteriaceae (*E. coli*, *K. pneumoniae*) and non-fermenters (*P. aeruginosa*, *A. baumannii*, and *S. maltophilia*) was conducted by recreating the human plasma PK exposure through IV administration of 2-g cefiderocol with a 3-hour infusion as shown in [Section 6.3](#). These studies confirmed the bactericidal efficacy using 75 %  $fT_{>MIC}$  up to an MIC of 4 µg/mL. In addition, as shown in [Section 6.2](#), the efficacy using rat lung infection models were evaluated by recreating human PK exposure through IV administration of 2-g cefiderocol with a 3-hour infusion compared with a 1-hour infusion. For clinical isolates with higher MICs to cefiderocol, the 3-hour infusion proved superior to the 1-hour infusion. From these results, this target of 75 %  $fT_{>MIC}$  was confirmed to be predictive of efficacy for all bacterial species.

## 6.2 Rat Lung Infection Model Based on Human Exposure Profile

With the bactericidal target established at 75 %  $fT_{>MIC}$ , Shionogi next examined the dosing regimen, specifically the infusion time, to optimize the PD of cefiderocol. A model of pneumonia was developed whereby immunocompetent rats were continuously connected to a computer controlled IV catheter to allow precisely regulated drug exposure and variable infusion durations. The exposure curve for cefiderocol measured in rat plasma was programmed to be similar to that in healthy human volunteers after administration of 2 g IV infusions over 1 or 3 hours (3-hour infusion shown in [Figure 9](#)). The therapeutic efficacy of cefiderocol under human exposure was then compared with that of other available antibiotics (ceftazidime and meropenem) in a series of studies using this model of rat lung infection caused by Gram-negative clinical isolates.

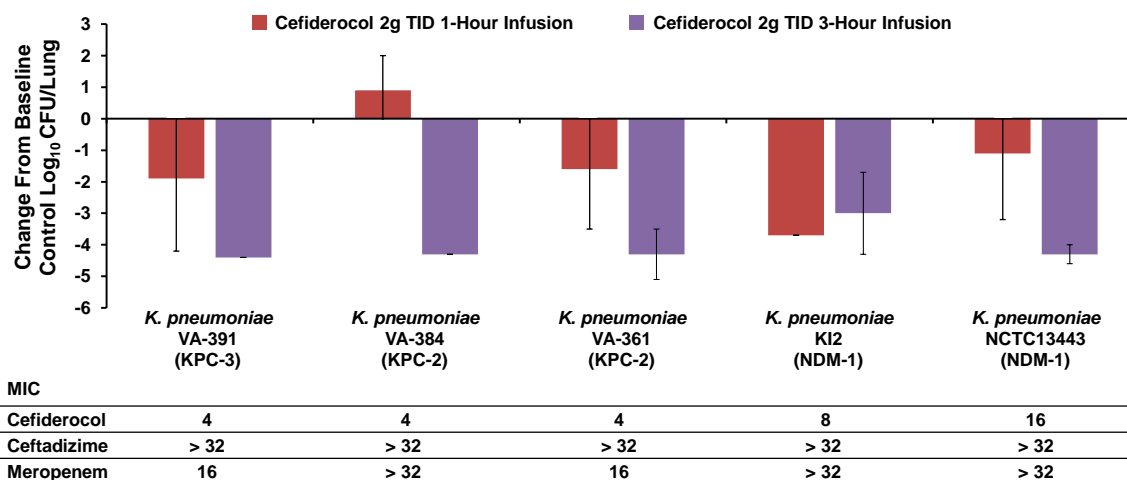
**Figure 9**      **Reproduction of Human Exposure (2 g Cefiderocol, Intravenous Administration With 3-h Infusion) in a Rat Lung Model**



PK, pharmacokinetics.

As shown in [Figure 10](#), the simulation of the 3-hour cefiderocol infusion produced better efficacy against MDR/CR strains, including NDM producers with MICs of 4 to 16 µg/mL, than the 1-hour cefiderocol infusion. Meropenem (a carbapenem) and ceftazidime (a cephalosporin) were ineffective against these pathogens. Bactericidal activity with the 3-hour infusion was observed for cefiderocol against the most problematic carbapenemases, KPC and NDM. These results suggested that the q8h IV administration of cefiderocol as a 3-hour infusion was likely to be effective against infections caused by CR strains including NDM producers, even if the strain had a cefiderocol MIC as high as 16 µg/mL.

**Figure 10**                      **Efficacy of Cefiderocol in Rat Lung Infection Models Reproducing the Human Pharmacokinetic Profile at 96 Hours**



CAZ, ceftazidime; q8h, every 8 hours; MEPM, meropenem; SD, standard deviation; tid, 3 times a day. Simulated human PK regimen: 2 g cefiderocol q8h as a 1-hour or 3-hour infusion, 1 g CAZ q8h as a 0.5-hour infusion, or 1 g MEPM q8h as bolus.

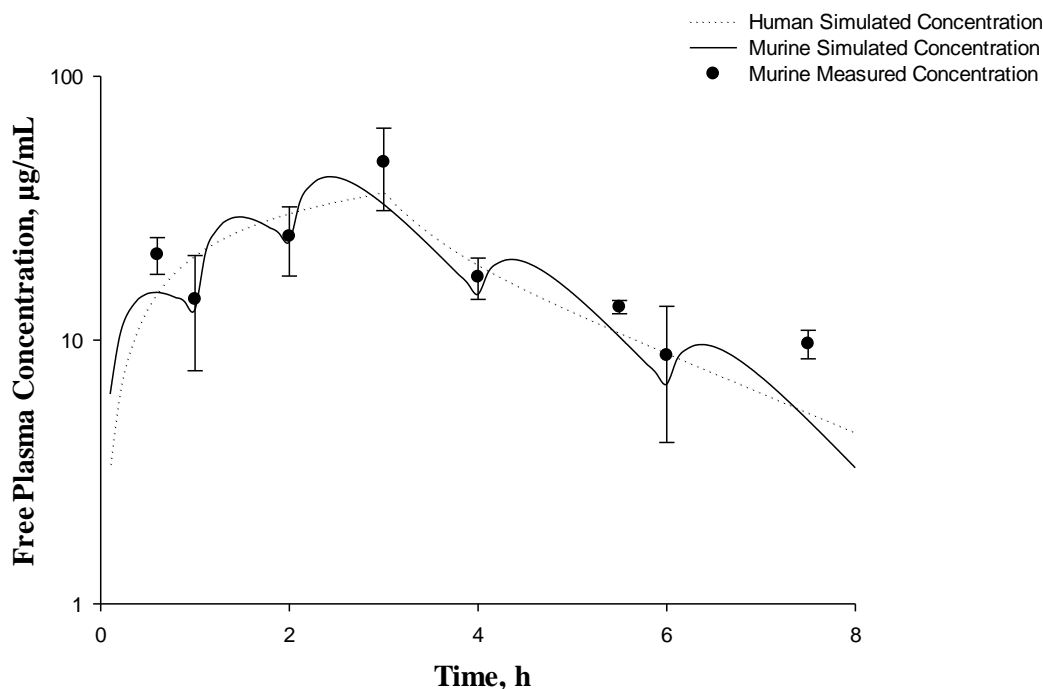
Viable cells evaluated in lungs 96 hours after infection.

Each bar represents the mean and SD.

### 6.3 Murine Thigh Infection Model Based on Human Exposure Profile

The standard model for assessing PK/PD is the neutropenic murine thigh model. This model was adapted to provide similar drug exposure in mice to the drug exposure in humans using the 2-g q8h dose. This was achieved by decreasing renal elimination and frequent dosing to provide an exposure curve as shown in [Figure 11 \(Ghazi 2018\)](#).

**Figure 11 Cefiderocol 2g q8h (3-h Infusion) Humanized Pharmacokinetic Profile in a Neutropenic Mouse Thigh Infection Model Compared With the Human Profile**



For murine measured concentration, dot = mean; whiskers = standard deviation.

The experiment then tested the efficacy of this drug exposure using 137 strains of bacteria selected to provide a broad range of MICs to cefiderocol (0.15 to  $\geq 64$   $\mu\text{g/mL}$ ). For bacteria with MICs to cefiderocol  $\leq 4$   $\mu\text{g/mL}$  (CLSI provisional breakpoint), 87% (79/91) showed static effect or bactericidal activity compared with initial inoculum and 97% (88/91) showed bactericidal activity compared with non-treatment groups *in vivo* (Table 5). Organisms with MICs of 8  $\mu\text{g/mL}$  showed variable response (33% or 50%) while those with MICs of  $\geq 16$   $\mu\text{g/mL}$  were less effective (0% or 29%). Importantly, the relationship between drug exposure and efficacy was the same regardless of the species of bacteria, including *P. aeruginosa* and *A. baumannii*.

**Table 5 Neutropenic Mice Thigh Infection Model With Humanized Dosing**

**(1) Efficacy compared with 24-hr non-treatment group**

MIC	No. of Strains Against Which CFDC Was Effective <sup>a</sup> /No. Total Strains							
	0.12	0.25	0.5	1	2	4	8	≥ 16
Enterobacterales	1/1	2/2	4/4	4/5	4/5	12/14	2/2	1/6
<i>P. aeruginosa</i>	0/0	2/2	5/5	7/7	1/2	4/4	0/1	0/0
<i>A. baumannii</i>	3/3	2/2	4/4	3/3	3/3	1/1	1/3	1/16
<i>S. maltophilia</i>	20/20	1/1	3/3	0/0	0/0	0/0	0/0	0/0
Total by MIC	24/24	7/7	16/16	14/15	8/10	17/19	3/6	5/22
Total MIC ≤ 4	86/91 (95 %): 87 % Enterobacterales, 95 % <i>P. aeruginosa</i> , 100 % <i>A. baumannii</i> , 100 % <i>S. maltophilia</i>						-	-

CFDC, cefiderocol; MIC, minimum inhibitory concentration.  
a. > 2-log reduction compared with no treatment for 24 hours.

**(2) Efficacy compared with initial inoculum**

MIC	No. of Strains Against Which CFDC Was Effective <sup>a</sup> /No. Total Strains							
	0.12	0.25	0.5	1	2	4	8	≥ 16
Enterobacterales	1/1	2/2	4/4	3/5	4/5	10/14	1/2	0/6
<i>P. aeruginosa</i>	0/0	1/2	5/5	6/7	1/2	4/4	0/1	0/0
<i>A. baumannii</i>	3/3	2/2	4/4	2/3	2/3	1/1	1/3	0/16
<i>S. maltophilia</i>	20/20	1/1	3/3	0/0	0/0	0/0	0/0	0/0
Total by MIC	24/24	6/7	16/16	11/15	7/10	15/19	2/6	0/22
Total MIC ≤ 4	79/91 (87 %): 77 % Enterobacterales, 85 % <i>P. aeruginosa</i> , 88 % <i>A. baumannii</i> , 100 % <i>S. maltophilia</i>						-	-

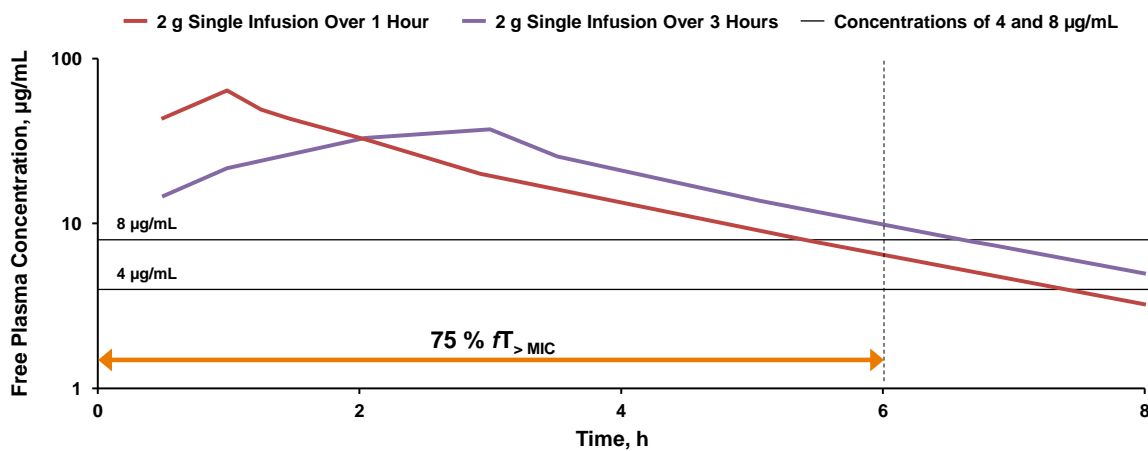
CFDC, cefiderocol; MIC, minimum inhibitory concentration.  
a. static effect or bactericidal efficacy compared with initial inoculum.

## 6.4 Human PK Profiles and Recommendation for Extended Infusion

A comparison of the %  $fT_{>MIC}$  for 1- and 3-hour infusions of cefiderocol 2g in healthy human subjects in Phase 1 Studies R2111 and R2116 demonstrates that the 3-hour infusion provides more time above target MICs than the 1-hour infusion (Figure 12).

Cefiderocol exhibits time-dependent anti-bacterial activity similar to other cephalosporins. Cefiderocol was administered as a 1-hour infusion in the cUTI study and had a similar safety profile to the comparator IMP/CS. The 3-hour infusion has a lower maximum plasma concentration ( $C_{max}$ ) but similar area under the concentration-time curve (AUC). Importantly, the 3-hour infusion extends the %  $fT_{>MIC}$  and optimizes the bactericidal activity of cefiderocol. The 3-hour infusion was used in Phase 1 studies without identification of new safety or tolerability events. There have been no identified differences in the safety profile between the 1- or 3-hour infusions, the 3-hour infusion is recommended to optimize the antibacterial activity of cefiderocol.

**Figure 12**                      **Pharmacokinetics of 1- and 3-Hour Infusions of Cefiderocol 2 g in Healthy Human Subjects in Studies R2111 and R2116**

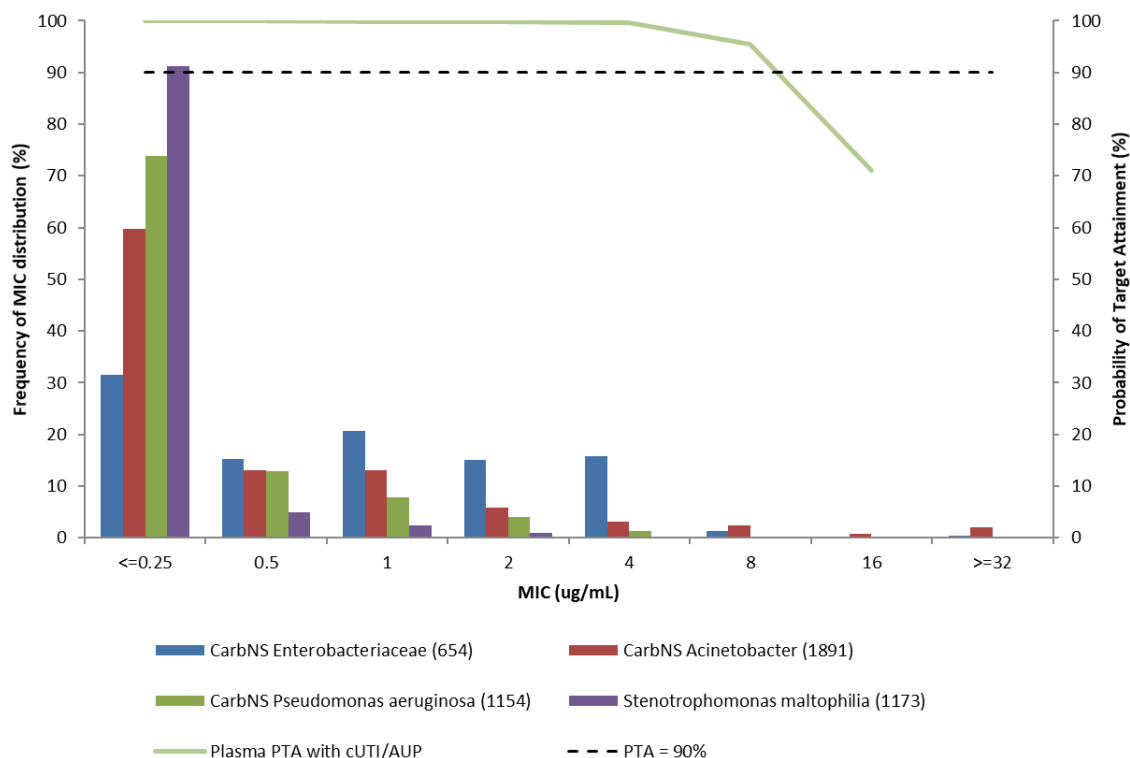


## 6.5 Probability of Target Attainment

To support cefiderocol dosing recommendations, PK/PD modeling and simulations were performed to estimate the probability of target attainment (PTA) for  $\geq 75\% fT_{>MIC}$  in patients with infections caused by Gram-negative bacteria.

A human population PK model was developed based on pooled data from 2 Phase 1 studies, the pivotal cUTI study, and the CREDIBLE-CR study. Monte-Carlo simulations using the population PK model were conducted to estimate PTA for the target of  $75\% fT_{>MIC}$  at the dose regimens that were based on renal function. For the estimation of PTA, creatinine clearance (CrCl) was simulated according to the proportion of patients in renal function groups in the CREDIBLE-CR study. The simulations suggested that the selected dose regimens of cefiderocol (2 g q8h over 3 hours with adjustment based on renal function) the probability would be greater than 90% against organisms with MICs of  $\leq 8 \mu\text{g/mL}$  (Figure 13 and Table 6).

**Figure 13**      **Probability of Target Attainment for 75 %  $fT_{>MIC}$  for 3-Hour Infusions of Cefiderocol 2 g q8h in cUTI Patients Versus Carbapenem Nonsusceptible Isolates**



MIC, minimum inhibitory concentration; PTA, probability of target attainment; q8h, every 8 hours. CrCl was simulated according to the proportion of patients in renal function groups (augmented, normal, mild, moderate, severe, end-stage renal disease = 21.3%, 12.7%, 20.0%, 28.0%, 11.3%, 6.7%, respectively) which was set based on CrCl from 150 patients in the CREDIBLE-CR study.

**Table 6**                      **Probability of Target Attainment for 75%  $fT_{>MIC}$  in cUTI Patients with Various Levels of Renal Function at Selected Dosage Regimens**

Target % $fT_{>MIC}$	Renal Function	Regimen <sup>a</sup>	% PTA at MIC, $\mu\text{g/mL}$						
			0.25	0.5	1	2	4	8	16
75 %	Augmented	2 g q6h	100	100	99.9	99.8	98.9	89.7	53.6
	Normal	2 g q8h	100	100	100	99.7	97.4	88.9	45.2
	Mild	2 g q8h	100	100	100	100	99.4	95.6	71.7
	Moderate	1.5 g q8h	100	100	100	100	100	98.9	82.0
	Severe	1 g q8h	100	100	100	100	100	99.2	90.7
	ESRD	0.75 g q12h	100	100	100	100	99.9	99.3	85.7

CrCl, creatinine clearance; CV, coefficient of variation; ESRD, end-stage renal disease; MIC, minimum inhibitory concentration; PTA, probability of target attainment; qXh, every X hours.

PK steady state was assumed. PTA is shown in percent (%).

Renal function based on CrCl level: augmented,  $\geq 120$  mL/min (120 to  $< 150 = 50\%$ ; 150 to  $< 200 = 30\%$ ;  $\geq 200 = 20\%$ ); normal, 90 to  $< 120$  mL/min; mild, 60 to  $< 90$  mL/min; moderate, 30 to  $< 60$  mL/min; severe, 15 to  $< 30$  mL/min; ESRD, 5 to  $< 15$  mL/min.

Body weight was assumed to be log-normal distributed with geometric mean of 72.4 kg and CV of 30 %.

a. With a 3-hour infusion.

The PTA in plasma and ELF for 75%, 90% and 100%  $fT_{>MIC}$  by infection site and renal function is presented in [Appendix 15.2](#). These simulations included PK measurements from patients with nosocomial pneumonia from the CREDIBLE CR study.

## 6.6 Conclusions of Nonclinical Efficacy and Pharmacokinetic/Pharmacodynamic Assessments

The efficacy of cefiderocol against Gram-negative MDR/CR pathogens was demonstrated in numerous animal models, including studies where the drug exposure in animals was the same as the human drug exposure over time. From these studies, 75%  $fT_{>MIC}$  was established as the PD target for cefiderocol to show bactericidal activity.

Animal studies demonstrated that the dosing regimen of cefiderocol 2 g q8h with a 3-hour infusion provides a longer period of exposures above the MIC than the same dose over a 1-hour infusion for MDR/CR pathogens. Based on these experiments, and consistent with the pharmacodynamic principles of  $\beta$ -lactam antibiotics, the 3-hour infusion time is recommended in the proposed label for cefiderocol.

With  $\geq 75\%$   $fT_{>MIC}$  as the efficacy target, PK/PD modeling and simulations showed a greater than 90% PTA for the recommended therapeutic doses, based on renal function, against all Gram-negative pathogens, including CRE and CR non-fermenters, with an MIC of  $\leq 4$   $\mu\text{g/mL}$ . This PTA specifically included and accounted for both impaired and augmented (ie, enhanced) renal function using data from both patients and healthy subjects.

## 7 NONCLINICAL SAFETY AND TOXICOLOGY

Safety pharmacology studies were conducted to evaluate the effects of cefiderocol on the central nervous system (CNS) in rats, the cardiovascular system in monkeys, and the respiratory system in rats. Convulsions were observed in rats and prolonged QT interval in monkeys at dosages far exceeding the recommended clinical regimen. These findings were species specific and not replicated in other studies of cardiac repolarization. Similar effects have not been observed in clinical studies, including the Thorough QT Study R2116 (See [Section 8.1](#)).

A full spectrum of toxicology studies with cefiderocol including single-dose and repeat dose toxicology, genotoxicity, reproductive and developmental toxicity, and phototoxicity studies, were performed in rats, mice, rabbits, monkeys, and guinea pigs. All these studies were conducted under the conditions that provided a systemic exposure or concentration of cefiderocol exceeding the systemic exposure in humans at the intended clinical dosing regimen (2 g infused over 3 hours three times daily), except for a guinea pig antigenicity study. Sufficient data were obtained to assess the possible risk of cefiderocol on human safety and no particular risk factors were identified to limit clinical use of cefiderocol for humans.

The results of the key safety pharmacology and repeat-dose toxicology studies and their estimated exposure ratios of animal to human are summarized in [Table 7](#) and [Table 8](#), respectively.

### 7.1 Effect on the Central Nervous System

In the rat CNS study, cefiderocol had little effect on the CNS at doses up to 0.5 g/kg, but after drug administration at 1 g/kg, the animals were lying in a prone position with decreases in motor activity and rectal temperature, suggesting that cefiderocol had inhibitory effects on the CNS. The safety margin in humans was estimated to be 10.6-fold between the completion of dosing ( $C_0$ ) at the no observed adverse effect level (NOAEL) in the rat CNS system study and the  $C_{max}$  in humans at the intended clinical dosing regimen. These findings rapidly disappeared in parallel with a decrease in plasma concentration of cefiderocol. No related finding such as sedation or hypothermia was observed in any clinical study.

Convulsions and subsequent deaths were observed in rat single-dose toxicity study, an in vivo micronucleus test in rats receiving 2 g/kg, and in a 3-month repeat-dose toxicity study at  $\geq 1.0$  g/kg/day. Therefore, a supplemental 3-month repeat-dose toxicity study in rats with doses of 0.5 and 0.75 g/kg, along with an electroencephalogram (EEG) and concomitant behavioral study, also in rats, were conducted to assess the convulsive liability of cefiderocol. No convulsions or deaths were observed at 0.75 g/kg in the supplemental 3-month repeat-dose toxicity study in rats and single IV doses of cefiderocol up to 0.75 g/kg caused no convulsions or changes in concomitant behavior and EEG in rats. The mean  $C_0$  of cefiderocol on Day 1 at 0.75 g/kg was 1280  $\mu\text{g/mL}$ , suggesting that the safety margin was approximately 14.3-fold of the  $C_{max}$  of cefiderocol in humans (89.7  $\mu\text{g/mL}$ ) at the intended clinical dosing regimen.

In monkeys, convulsions were not noted in any study at 1 g/kg/day, at which the  $C_0$  value (2300 to 2600  $\mu\text{g/mL}$  on the last day of dosing in the repeat-dose toxicity studies) was approximately 26- to 29-fold of the  $C_{\text{max}}$  value in humans at the intended clinical dosing regimen.

The proconvulsive effects of cefiderocol and reference substances (cefazolin sodium hydrate [CEZ], cefepime [CFPM], ceftazidime [CAZ], and IPM) were investigated following intracerebroventricular injections in mice. Based on the 95 % CI ranges, the proconvulsive effect of cefiderocol following intracerebroventricular (ICV) injection in mice is weaker than that of IPM, comparable to those of CEZ and CFPM, and stronger than that of CAZ.

The convulsive potential of  $\beta$ -lactam antibiotics is generally considered to be related to the inhibition of gamma-aminobutyric acid (GABA) receptor binding ([ICH 2017](#), [Antoniadis 1980](#)). Results from the rat toxicity studies suggested that the convulsions were induced when the plasma concentration of cefiderocol was elevated to extremely high levels.

There has been one case of convulsions in the clinical studies in which a cefiderocol recipient with a history of epilepsy had a single seizure that occurred on treatment Day 7; treatment was completed uneventfully for a further 3 days.

## 7.2 Effect on the Cardiovascular System

The effect of cefiderocol on potassium currents in human embryonic kidney-293 cells stably expressing human ether-à-go-go-related gene (hERG) channels was investigated using the whole-cell patch clamp technique. Cefiderocol had little effect on the myocardial action potential in papillary muscles and hERG current up to 1.5 mg/mL, which is 34.7-fold of the free  $C_{\text{max}}$  value in humans ( $\leq 43.2 \mu\text{g/mL}$ ) at the intended clinical dosing regimen.

Cefiderocol had no effect on the monkey cardiovascular system at doses up to 0.3 g/kg. However, at 1.0 g/kg, cefiderocol caused an elevation of mean blood pressure and a prolonged corrected QT interval (QTc). The safety margin in humans was estimated to be 10.1-fold between the completion of dosing ( $C_0$ ) at the NOAEL in the monkey cardiovascular system study and the  $C_{\text{max}}$  in humans at the intended clinical dosing regimen. Prolongation of QTc was also noted in repeat-dose toxicity studies in monkeys at 0.6 and/or 1.0 g/kg/day.

No serious cardiac arrhythmia or adverse finding in cardiac tissue was observed after 3 months of dosing with cefiderocol in toxicology studies in monkeys. In a thorough QT/QTc study conducted in human subjects, cefiderocol showed no clinically meaningful change in cardiovascular function, even at supratherapeutic doses. Under the intended clinical dosing regimen, the risk for QTc prolongation, elevation of blood pressure, and relevant cardiac events is low. Similar adverse effects have not been observed in clinical studies, including the Thorough QT Study R2116 (See [Section 8.1](#)).

The results of the key safety pharmacology studies are summarized in Table 7. Other nonclinical studies revealed no remarkable findings.

**Table 7 Results of Key Safety Pharmacology Studies**

Study		Dose/Concentration (Route, Dosing Duration)	Major Findings	Animal to Human Ratio
Safety pharmacology	Central nervous system study (rat)	250, 500, 1000 mg/kg (IV, 30 min/animal)	1000 mg/kg: prone position, decreased motor activity and rectal temperature	10.6 <sup>a</sup>
	Respiratory system study (rat)	250, 500, 1000 mg/kg (IV, 30 min/animal)	None	> 20.4 <sup>b</sup>
	Cardiovascular system study (monkey)	100, 300, 1000 mg/kg (IV, 60 min/animal)	1000 mg/kg: elevation of blood pressure, QTc prolongation	10.1 <sup>c</sup>
	Action potential duration study (in vitro)	0.15, 0.5, 1.5 mg/mL (in vitro)	None	> 34.7 <sup>d</sup>
	hERG study (in vitro)	0.15, 0.5, 1.5 mg/mL (in vitro)	IC <sub>50</sub> > 1.5 mg/mL	> 34.7 <sup>d</sup>
Follow-up safety pharmacology	Behavioral study for convulsion (mouse)	10, 25, 50, 100 µg/ mouse (ICV)	CD <sub>50</sub> = 23.44 µg/mouse	N/A
	EEG and behavioral study for convulsion (rat)	500, 750 mg/kg (IV, 30 min/animal)	None	14.3 <sup>e</sup>

CD<sub>50</sub>, dose level to induce convulsions in 50 % of mice (50 % convulsive dose); C<sub>0</sub>, plasma concentration at the completion of dosing; C<sub>max</sub>, maximum plasma concentration; EEG, electroencephalogram/electroencephalography; hERG, human ether-à-go-go-related gene; IC<sub>50</sub>, 50 % inhibitory concentration; ICV, intracerebroventricular; IV, intravenous; N/A, not applicable; tid, 3 times a day.

a. The ratio of the C<sub>0</sub> value at 500 mg/kg/day on the first day of dosing in the rat 2-week toxicity study (952 µg/mL) to the C<sub>max</sub> value of cefiderocol in humans (89.7 µg/mL) at the intended clinical dosing regimen (2 g, infused over 3 hours, tid).

b. The ratio of the C<sub>0</sub> value at 1000 mg/kg/day on the first day of dosing in the rat 2-week toxicity study (1830 µg/mL) to the C<sub>max</sub> value of cefiderocol in humans (89.7 µg/mL) at the intended clinical dosing regimen (2 g, infused over 3 hours, tid).

c. The ratio of the C<sub>0</sub> value at 300 mg/kg in the monkey telemetry study (907 µg/mL) to the C<sub>max</sub> value of cefiderocol in humans (89.7 µg/mL) at the intended clinical dosing regimen (2 g, infused over 3 hours, tid).

d. The ratio of the no-effect-concentration level (1.5 mg/mL) to the free C<sub>max</sub> value of cefiderocol in humans (43.2 µg/mL) at the intended clinical dosing regimen (2 g, infused over 3 hours, tid), calculated from the protein binding ratios of the cefiderocol sodium drug product in human plasma (51.8 %).

e. The ratio of the C<sub>0</sub> value at 750 mg/kg/day on the first day of dosing in the rat 3-month toxicity study (1280 µg/mL) to the C<sub>max</sub> value of cefiderocol in humans (89.7 µg/mL) at the intended clinical dosing regimen (2 g, infused over 3 hours, tid)

### 7.3 Toxicology Studies

Key toxicology studies with cefiderocol are summarized in Table 8. In single dose toxicology studies, acute symptoms including convulsions and abnormal respiration, and death were noted at 2 g/kg once daily. However, neither mortality nor acute symptoms were noted in any animal at 1 g/kg given twice a day (bid).

In 3-month repeat-dose toxicology studies in rats, convulsions were noted with cefiderocol  $\geq 1$  g/kg/day. Convulsions occurred around dosing and the incidence of convulsions was sporadic during the study. Almost all animals died following convulsions. Overall, the NOAEL was judged to be 750 mg/kg/day in rats treated with the cefiderocol for 3 months. All other changes were considered non-adverse based on their properties, severities, and predictability to humans.

In 1-month and 3-month repeat-dose toxicity studies at 0 to 1 g/kg/day in monkeys, no deaths nor moribund states were observed. Prolongation of QTc was observed in some animals in the 0.6-g/kg/day and 1-g/kg/day groups. Vomiting was observed at the highest dose. All other changes were considered non-adverse. The NOAEL was judged to be 300 mg/kg/day in the 1-month study and 100 mg/kg/day in the 3-month study.

No particular risk factors to limit clinical use of cefiderocol for humans were identified in these toxicology studies. Other nonclinical studies revealed no remarkable findings.

**Table 8 Summary of the Results of the Key Repeat-Dose Toxicology Studies**

Study	Dose/ Concentration	Major Findings	Animal to Human Ratio at NOAEL
Rat, 2-week toxicity study	250, 500, 1000 mg/kg/day (IV)	<u>NOAEL</u> 1000 mg/kg/day <u>Non-adverse finding</u> $\geq 500$ mg/kg/day: cecum, macroscopic dilatation and microscopic atrophy of the mucosa; kidney, hyaline droplets in proximal tubules	$C_0^a$ : 19.0 to 22.1 $AUC^b$ : 0.9 to 1.2
Rat, 1-month toxicity study	300, 1000, 1500 mg/kg/day (IV)	<u>NOAEL</u> 1500 mg/kg/day <u>Non-adverse finding</u> $\geq 300$ mg/kg/day: cecum, macroscopic dilatation and microscopic hypertrophy of the mucosal epithelium; kidney, hyaline droplets in proximal tubules; spleen, development of germinal centers, slightly low erythrocyte parameters	$C_0^a$ : 32.6 to 34.7 $AUC^b$ : 1.7 to 1.8

Study	Dose/ Concentration	Major Findings	Animal to Human Ratio at NOAEL
Rat, 3-month toxicity study <sup>a</sup> and supplemental 3-month toxicity study (specific evaluation for convulsions) <sup>b</sup>	300 <sup>a</sup> , 500 <sup>b</sup> , 750 <sup>b</sup> , 1000 <sup>a</sup> , 1500 <sup>a</sup> mg/kg/day (IV)	<u>NOAEL</u> <sup>a,b</sup> 750 mg/kg/day <u>Adverse finding</u> <sup>a,b</sup> ≥ 1000 mg/kg/day: convulsions and deaths <u>Non-adverse finding</u> <sup>a</sup> ≥ 300 mg/kg/day: cecum, macroscopic dilatation and microscopic hypertrophy of the mucosal epithelium; kidney, hyaline droplets in proximal tubules; spleen, development of germinal centers ≥ 1000 mg/kg/day: slightly low erythrocyte parameters	C <sub>0</sub> <sup>a</sup> : 16.7 to 17.9 AUC <sup>b</sup> : 0.8 to 0.9
Monkey, 2-week toxicity study	100, 300, 1000 mg/kg/day (IV)	<u>NOAEL</u> 300 mg/kg/day <u>Adverse finding</u> 1000 mg/kg/day: QTc prolongation, local irritation at injection site <u>Non-adverse finding</u> ≥ 100 mg/kg/day: kidney, hyaline droplets in proximal tubules 1000 mg/kg/day: slightly low erythrocyte parameters, vomiting	C <sub>0</sub> <sup>a</sup> : 8.6 AUC <sup>b</sup> : 1.1 to 1.2
Monkey, 1-month toxicity study	100, 300, 600, 1000 mg/kg/day (IV)	<u>NOAEL</u> 300 mg/kg/day <u>Adverse finding</u> ≥ 600 mg/kg/day: QTc prolongation 1000 mg/kg/day: vomit, low erythrocyte parameters and PLT <u>Non-adverse finding</u> ≥ 100 mg/kg/day: kidney, hyaline droplets in proximal tubules	C <sub>0</sub> <sup>a</sup> : 9.0 to 9.4 AUC <sup>b</sup> : 1.2
Monkey, 3-month toxicity study	100, 300, 1000 mg/kg/day (IV)	<u>NOAEL</u> 100 mg/kg/day <u>Adverse finding</u> ≥ 300 mg/kg/day: low erythrocyte parameters, local irritation at injection site 1000 mg/kg/day: QT/QTc prolongation, vomit <u>Non-adverse finding</u> ≥ 100 mg/kg/day: kidney, hyaline droplets in proximal tubules	C <sub>0</sub> <sup>a</sup> : 3.3 to 3.4 AUC <sup>b</sup> : 0.4

AUC, Area under the concentration-time curve; C<sub>0</sub>, plasma concentration at the completion of dosing; C<sub>max</sub>, maximum plasma concentration; IV, intravenous; NOAEL, no observed adverse effect level; qd, once a day; tid, three times a day.

a. The ratio of the C<sub>0</sub> value of cefiderocol on the last day of dosing in each toxicity study to the C<sub>max</sub> value of cefiderocol in humans (89.7 µg/mL) at the intended clinical dosing regimen (2 g, infused over 3 hours, tid), the C<sub>max</sub> value of cefiderocol in the clinical study (2 g infused over 3 hours, qd).

b. The ratio of the AUC<sub>total</sub> value of cefiderocol on the last day of dosing in each toxicity study to the AUC<sub>0-inf</sub> value of cefiderocol in humans (1158.3 µg/mL) at the intended clinical dosing regimen (2 g, infused over 3 hours, tid), 3-fold the AUC<sub>0-inf</sub> value of cefiderocol in the clinical study (2 g infused over 3 hours, qd).

## 7.4 Nonclinical Safety Conclusions

Cefiderocol is a member of the cephalosporin class with a typical safety profile. No respiratory effect was observed in animal models. A monkey cardiovascular study showed QT prolongation at 10.1-fold the  $C_{\max}$  value in humans (89.7  $\mu\text{g/mL}$ ) at the intended clinical dosing regimen, but this was ruled out as a concern by the thorough QT Study R2116 (See [Section 8.1](#)). Convulsions were observed in animal studies, but only at high rates of exposure; approximately 24 times the human exposure at the intended clinical dosing regimen. Convulsions at high serum concentrations may be a class effect of  $\beta$ -lactam antibiotics related to inhibition of GABA receptor binding. In clinical studies with cefiderocol, only 1 seizure was observed in a patient known to have epilepsy (See [Section 9.6.4.6](#)) and labeling for this potential has been proposed by Shionogi. No particular risk factors were identified in these toxicology studies that would limit clinical use of cefiderocol for humans. There was no indication from the clinical pharmacology studies or clinical trials of unacceptable risk for use of cefiderocol at the intended dosing regimen.

## 8 CLINICAL PHARMACOLOGY

Six clinical pharmacology studies were conducted to support the limited-use cUTI indication for cefiderocol (Table 9). A total of 212 healthy adult volunteers or patients with varying degrees of renal impairment received single 0.1g to 4-g doses of cefiderocol or multiple 1- or 2-g doses of cefiderocol q8h for 10 days. Cefiderocol was administered as an IV infusion over 1 hour in 4 studies (Studies R2111, R2112, R2113, and R2114) and as an IV infusion over 3 hours in 2 studies (Studies R2115 and R2116). The clinical pharmacology studies were conducted to characterize the PK profile, assess the safety and tolerability profile, and inform dosing recommendations for cefiderocol.

Through these studies, the PK of cefiderocol was shown to be predictable and supports the recommended dosing regimen.

**Table 9 Clinical Pharmacology Studies and Pivotal cUTI Study**

Study ID/ Type (Country)	Design/Objectives	Subjects	Dosages, mg
<b>R2111/</b> Phase 1 SAD/MAD study (Japan)	Randomized, Double-blind placebo-controlled SAD/MAD study/Safety, tolerability, and PK	Healthy adults	Part 1: CFDC 100, 250, 500, 1000, 2000 mg, or matching placebo infused over 1 hour Part 2: CFDC 1000, 2000 mg, or matching placebo infused over 1 hour q8h
<b>R2112/</b> Phase 1 Intrapulmonary PK study (Japan)	Open-label BAL, single measurement per subject/Intra- pulmonary PK and safety	Healthy adults	CFDC 2000 mg infused over 1 hour
<b>R2113/</b> Phase 1 Renal impairment study (US)	Open-label single dose study except for hemodialysis patients/Influence of renal impairment and dialysis clearance on PK	Healthy adults and mild, moderate, severe renal impairment and hemodialysis	CFDC 1000 mg infused over 1 hour
<b>R2114/</b> Phase 1 Mass balance study (US)	Open-label single- dose study /Characterize metabolism, excretion, and mass balance	Healthy adult males	[ <sup>14</sup> C]-CFDC 1000 mg (~100 µCi) infused over 1 hour
<b>R2115/</b> Phase 1 3-Part DDI study (US)	Open-label, randomized 2- sequence, 2-period crossover study/PK, safety, and tolerability	Healthy adults	Part 1,2 and 3: CFDC 2000 mg infused over 3 hours q8h (3, 6, and 9 doses, respectively) Part 1: Furosemide 20 mg Part 2: Metformin 1000 mg Part 3: Rosuvastatin 10 mg

Study ID/ Type (Country)	Design/Objectives	Subjects	Dosages, mg
<b>R2116/</b> Phase 1 Thorough QT/QTc study (US)	Randomized, placebo- and positive-controlled crossover study/ Part 1: Safety, tolerability, and PK Part 2: Effect on the QTcF interval	Healthy adults	Part 1: CFDC 3000 mg (Group A), 4000 mg (Group B) or matching placebo infused over 3 hours Part 2: CFDC 2000, 4000 mg, or matching placebo infused over 3 hours once Moxifloxacin 400 mg
<b>cUTI/</b> Phase 2 Pivotal study (US, Europe, Japan)	Randomized, positive-controlled study/Efficacy and safety	Hospitalized adults with cUTI	CFDC 2000 mg infused over 1-hour q8h <sup>a</sup> IPM/CS: 1000 mg infused over 1-hour q8h <sup>a</sup>

BAL, bronchoalveolar lavage; CFDC, cefiderocol; cUTI, complicated urinary tract infection; DDI, drug-drug interaction; IPM/CS, imipenem/cilastatin; MAD, Multiple ascending dose; PK, pharmacokinetic; q8h, every 8 hours; QTcF, Corrected QT interval by Fridericia; SAD, single ascending dose; US, United States.

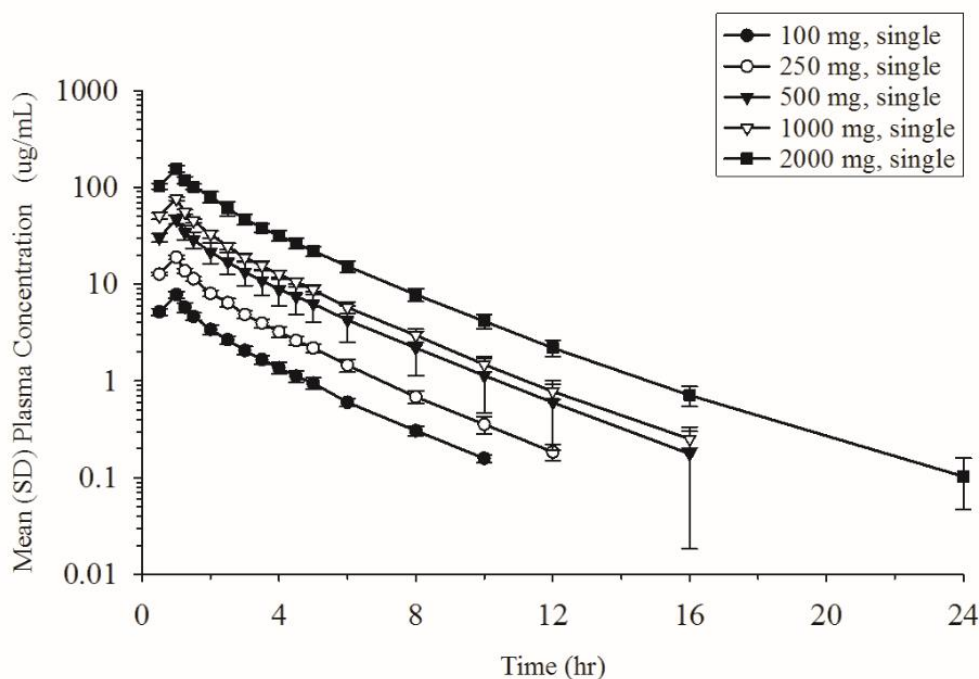
a. Dose (CFDC, 750 to 2000 mg; IPM/CS, 25 to 1000 mg) or interval (6 to 8 hours) based on renal function or body weight.

In addition, a population PK analysis was performed to describe the plasma concentration of cefiderocol and to evaluate the effects of influencing factors on cefiderocol PK, based on the pooled data from 2 Phase 1 studies, the Phase 2 cUTI study, and the Phase 3 CREDIBLE-CR study, those with impaired renal function, patients with cUTI and acute uncomplicated pyelonephritis (AUP), and patients with infections caused by CR pathogens (Studies R2111, R2113, R2121, and R2131).

## 8.1 Key Findings for the Clinical Pharmacology of Cefiderocol

The PK of cefiderocol is linear in the tested dose range of 0.1 to 4 g. The  $C_{max}$  and AUC of cefiderocol increased in a dose-proportional manner within the dose range of 0.1 to 2 g in Study R2111 (Figure 14) and 2 to 4 g in Study R2116.

**Figure 14**      **Mean Plasma Concentrations of Cefiderocol Following Single-Dose Administration Infused over 1 Hour**



SD, standard deviation.

After administration of 1- and 2-g doses of cefiderocol q8h over a 1-hour infusion, no accumulation for the  $C_{max}$  or AUC over the dosing interval was observed in Study R2111. Steady state was attained within 1 day after the start of multiple-dose administration.

The plasma protein binding ratios for cefiderocol over concentrations of 1 to 1000  $\mu\text{g/mL}$  ranged from 40.8% to 60.4%. The binding at cefiderocol concentrations of 10  $\mu\text{g/mL}$ , which was close to the concentrations at 8 hours following a single 2-g dose infused over 3 hours (ie, geometric mean 11.5  $\mu\text{g/mL}$ ) (Study R2116), was 57.8%.

The epithelial lining fluid (ELF) concentration profile appeared to be parallel to the plasma concentration profile in healthy subjects (Study R2112). The AUC ratios of ELF and alveolar macrophage concentrations to free drug in plasma were 0.239 and 0.0419, respectively.

After administration of a single 2-g dose of cefiderocol infused over 3 hours, the geometric mean volume of distribution during the terminal elimination phase ( $V_z$ ) was 18.0 L (coefficient of variation [CV] 18.1%; Study R2116).

The elimination half-life ( $t_{1/2,z}$ ) of cefiderocol is 2 to 3 hours. After administration of a single 2 g dose of cefiderocol infused over 3 hours in Study R2116, the  $t_{1/2,z}$  of cefiderocol was 2.4 hours. A similar  $t_{1/2,z}$  of 2.74 hours was estimated after administration of a single 2 g dose of cefiderocol infused over 1 hour in Study R2111.

Metabolism of cefiderocol is minor prior to excretion. Cefiderocol is mainly excreted in an unchanged form in urine. After administration of a single 1-g dose of [<sup>14</sup>C]-cefiderocol infused over 1 hour, the majority of total radioactivity in plasma was accounted for intact drug in Study R2114. Metabolite profiling demonstrated that unchanged cefiderocol accounted for ~92.3% of total radioactivity AUC in plasma and ~90% of administered dose in urine. No metabolites accounted for greater than 10% in either plasma or urine. The single- and multiple-dose Study R2111 and the renal impairment Study R2113 also demonstrated cefiderocol was primarily eliminated by renal excretion, with no major metabolites in either plasma or urine in the single- and multiple-dose Study R2111.

Dose adjustment in patients with hepatic impairment is not required considering that the primary route of elimination for cefiderocol is through renal excretion.

The clearance of cefiderocol was dependent on renal function and the AUC of cefiderocol increased with decreasing renal function (Study R2113).

Cefiderocol did not interfere with drug interactions via cytochrome P (CYP) enzymes and drug transporters. In the *in vitro* study using human liver microsomes, no concentration- or time-dependent inhibitions by cefiderocol were observed for CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4, indicating that cefiderocol is not expected to affect the PK of co-administered drugs that are substrates of these CYP enzymes. No significant induction by cefiderocol at concentrations corresponding to plasma concentrations associated with the intended clinical dosing regimen of cefiderocol was observed for CYP1A2, 2B6, and 3A4, indicating that cefiderocol is not expected to affect the PK of co-administered drugs that are substrates of these CYP enzymes.

In the *in vitro* studies using human transporter expressing cells, cefiderocol was not a substrate of organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT)2, multidrug and toxin extrusion (MATE)1, MATE2-K, P glycoprotein (P-gp), or breast cancer resistance protein (BCRP), indicating that co-administration of inhibitors for these transporters are not expected to influence the PK of cefiderocol.

In the *in vitro* studies using human transporter-expressing cells, Caco-2 cells, or bile salt export pump (BSEP)-expressing vesicles, cefiderocol showed no significant inhibitory effect on OAT polypeptide (OATP)1B1, MATE1, P-gp, BCRP, or BSEP, indicating that cefiderocol is not expected to affect the PK of co-administered drugs that are substrates of these transporters.

As cefiderocol could potentially inhibit the OAT1, OAT3, OCT1, OCT2, OATP1B3, and MATE2-K transporters, clinical drug-drug interaction (DDI) Study R2115 was conducted to investigate the potential inhibitory effects of cefiderocol on the PK of substrates for these transporters. Cefiderocol did not increase the C<sub>max</sub> or AUC of furosemide (for OAT1 and OAT3) and metformin (for OCT1, OCT2, and MATE2-K). Cefiderocol increased the C<sub>max</sub> and AUC of rosuvastatin (for OATP1B3) by 1.28-fold (90 % CI: 1.12,

1.46) and 1.21-fold (90 % CI: 1.08, 1.35), respectively. These results suggest no clinically significant DDI potential via these transporters.

Dosing with cefiderocol did not prolong the QT interval at concentrations up to 4 g with 1-hour infusion times. In the thorough QT/QTc Study R2116 comparing single doses of cefiderocol 2- (therapeutic) and 4-g (supratherapeutic) with placebo and moxifloxacin 400 mg as a positive control, the point estimates of least squares means of time-matched placebo- and baseline-adjusted QTcF (ddQTcF) interval for both the 2- and 4-g doses of cefiderocol were  $\leq 5$  msec and the upper bound of the 90 % CI were  $\leq 10$  msec at all time points after initiation of the infusion. With moxifloxacin treatment, a prolongation of the QTcF interval was observed for all time points from 1 to 10 hours postdose, with the lower bound of the 90 % CI of least squares means in the ddQTcF  $> 5$  msec. Overall, cefiderocol met the criteria stipulated in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E14 Guidance for Industry (2005) associated with a negative thorough QT/QTc study.

The PK of cefiderocol was similar between Japanese and Caucasian subjects in the phase 1 studies. Population PK analysis showed that no adjustment of cefiderocol dose appears to be necessary based on age, sex, body weight, or race (White vs. Non-White).

No serious or clinically significant adverse event (AE) was observed in multiple dosing of 2 g q8h for 10 days. Based on the clinical pharmacology studies, cefiderocol was well tolerated at 2 g q8h, with a safety profile similar to other cephalosporins.

## **8.2 Population Pharmacokinetics with Patients in the Phase 1 Studies, the Phase 2 cUTI Study, and the Phase 3 CREDIBLE-CR Study**

### **8.2.1 Population PK Model**

A population PK analysis was performed to describe the plasma concentration of cefiderocol and to evaluate the effects of influencing factors on cefiderocol PK, based on the pooled data from 2 Phase 1 studies, the Phase 2 cUTI study, and the Phase 3 CREDIBLE-CR study in healthy subjects, those with impaired renal function, patients with cUTI and AUP, and patients with infections caused by CR pathogens (Studies R2111, R2113, R2121, and R2131). A total of 2934 cefiderocol concentrations from 406 subjects (91 subjects without infection, 238 patients in the Phase 2 cUTI study, and 77 patients in the CREDIBLE-CR study) were included in the population PK analysis. Nonlinear mixed effects modelling was performed using NONMEM<sup>®</sup>. A 3-compartmental model was used as a structural PK model. An exponential error model was used for interindividual variability, and proportional error model was used for intraindividual variability.

For model building, age, body weight, sex (male, female), albumin, AST, ALT, total bilirubin, baseline CrCl, time-varying CrCl, race/ethnicity ("White" or "non-White"), infection disease (no infection, hospital acquired pneumonia/ventilator-associated pneumonia/healthcare-associated pneumonia (HAP/VAP/HCAP), blood stream infection

(BSI)/sepsis, or cUTI/AUP), and ventilation (with or without) were each tested as a covariate on clearance (CL). Age, body weight, sex, albumin, race/ethnicity, infection disease, and ventilation (with or without) were each tested as a covariate on the volume of distribution in the central compartment (V1). Body weight was tested as a covariate on the volume of distribution in the peripheral compartment (V2).

The parameter estimates of the final population PK model are presented in Table 10. Overall, CrCl was the most significant covariate on CL. The effects of body weight were significant on V1 and V2. In addition, HAP/VAP/HCAP status and cUTI/AUP status in the cUTI study were significant on CL. Infection sites in each study were significant on V1.

**Table 10 Parameter Estimates of Final Population PK Model of Cefiderocol for Patients Caused by CR Pathogens**

Parameter	Estimate (% RSE)
CL (L/h)	
Typical CL	4.10 (2.2)
Effect of CrCl	0.660 (3.8)
Effect of HAP/VAP/HCAP	0.815 (7.0)
Effect of cUTI/AUP in cUTI study	1.27 (3.4)
V1 (L)	
Typical V1	7.77 (3.1)
Effect of body weight	0.761 (10.5)
Effect of HAP/VAP/HCAP	2.06 (11.7)
Effect of BSI/sepsis	2.20 (17.2)
Effect of cUTI in CREDIBLE-CR study	1.84 (9.6)
Effect of cUTI/AUP in cUTI study	1.36 (4.8)
Q2 (L/h)	5.84 (6.3)
V2 (L)	
Typical V2	5.40 (3.6)
Effect of body weight	0.761 (10.5)
Q3 (L/h)	0.112 (18.6)
V3 (L)	0.746 (9.3)
Interindividual variability	
CV % for CL	33.3 (13.9)
CV % for V1	44.9 (25.4)
CV % for V2	38.1 (37.1)
Intraindividual variability	
CV % for proportional error	15.7 (5.5)

AUP, acute uncomplicated pyelonephritis; BSI, blood stream infection; CL, total clearance; CrCl, creatinine clearance estimated by Cockcroft-Gault equation; cUTI, complicated urinary tract infection; CV, coefficient of variation; HAP, hospital acquired pneumonia; HCAP, health-care associated pneumonia; Q2, Q3 = apparent intercompartmental clearance; RSE, relative standard error; V1, volume of distribution in the central compartment; V2, V3, volume of distribution in the peripheral compartment; VAP, ventilator-associated pneumonia.

If CrCl < 200 mL/min then  $CL = 4.10 \times (CrCl/87.0)^{0.660} \times 0.815^{HAP/VAP/HCAP} \times 1.27^{cUTI/AUP}$

If CrCl ≥ 200 mL/min then  $CL = 4.10 \times (200/87.0)^{0.660} \times 0.815^{HAP/VAP/HCAP} \times 1.27^{cUTI/AUP}$

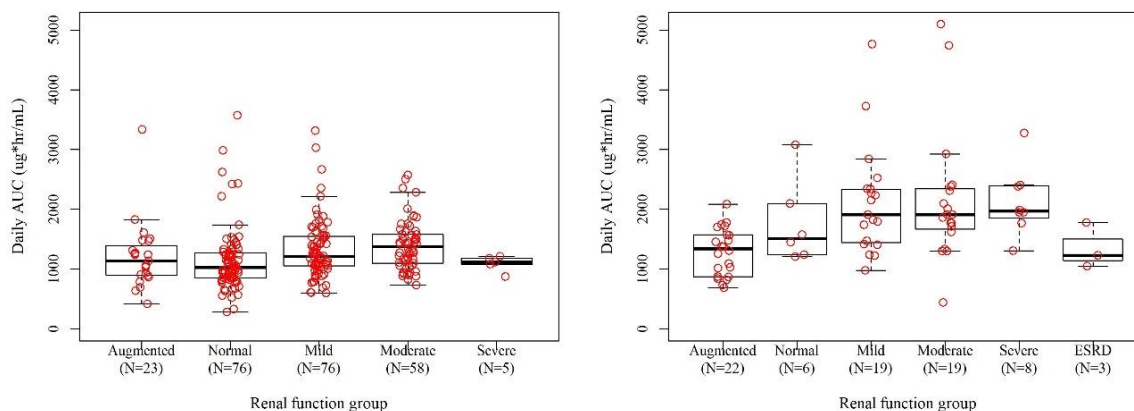
$V1 = 7.77 \times (body\ weight/72.4)^{0.761} \times 2.06^{HAP/VAP/HCAP} \times 2.20^{BSI/sepsis} \times 1.84^{cUTI\ (CR)} \times 1.36^{cUTI/AUP}$

$V2 = 5.40 \times (body\ weight/72.4)^{0.761}$

## 8.2.2 Comparison of Exposure of Cefiderocol among Patients with Various Levels of Renal Function

Daily AUC in patients in the cUTI study and CREDIBLE-CR study are separately presented by renal function group with the proposed dose adjustment in Figure 15; the left hand figure presents data for the cUTI study and the right hand figure presents data for the CREDIBLE-CR study. Daily AUC values were similar among renal function groups in the cUTI study. Daily AUC values appeared to be lower in patients with augmented renal function than those in the patients with other renal function. However, the Monte-Carlo simulations demonstrated a higher PTA was achieved in patients with augmented renal function (Table 6), suggesting the difference in AUC would not be clinically relevant. A dose adjustment based on CrCl is recommended to provide adequate exposure in patients with differing renal functions.

**Figure 15** Daily AUC by Renal Function with Proposed Dose Adjustment Based on Renal Function in cUTI (Left) and CREDIBLE-CR (Right)



AUC, area under the plasma concentration-time curve

Left: patients in the cUTI study. Right: patients in the CREDIBLE-CR study.

Renal function based on CrCl level: augmented,  $\geq 120$  mL/min; normal, 90 to < 120 mL/min; mild, 60 to < 90 mL/min; moderate, 30 to < 60 mL/min; severe, 15 to < 30 mL/min; ESRD, < 15 mL/min.

Dose regimens: augmented, 2 g q6h; normal, 2 g q8h; mild, 2 g q8h; moderate, 1.5 g q8h; severe, 1 g q8h; ESRD, 0.75 g q12h.

## 8.3 Proposed Dosing Regimens for Cefiderocol

The selection of a dose and dosing regimen for antibiotics is often based on empirical evidence from Phase 1 and 2 clinical trials. Rigorous PK/PD analyses are often performed after the drug is marketed. The rationale for the dose selection in humans for cefiderocol was based on the establishment of the PD target of percentage of time above MIC for free drug ( $\% fT_{>MIC}$ ) in animal infection models that included target pathogens, followed by estimation of the PTA using data from human PK in healthy subjects during Phase 1, confirmation of PK/PD in animal infection models using human drug exposure, optimization of PD with extended drug infusion from 1 to 3 hours, confirmation of PK in patients enrolled in the cefiderocol clinical trials, and inclusion of patient data to calculate the PTA.

Based on the PK/PD modeling described in [Section 6](#) and the results of the clinical pharmacology program, a cefiderocol dosing regimen of 2 g q8h with 3-hour infusion is proposed for patients with normal renal function. The recommended 3-hour infusion time provides a longer duration of plasma drug exposure concentration that exceeds the MIC of resistant pathogens. A reduced dose and/or extended dosing interval is recommended for all patients with impaired renal function, and a more frequent dose of every 6 hours may be used for patients with augmented (ie, enhanced) renal clearance (ARC) (Table 11).

**Table 11 Recommended Dosing for Patients Based on Renal Function**

Renal Function	Dose	Frequency	Infusion Time
<b>Patients with normal renal function</b> (CrCl 90 to < 120 mL/min)	2 g	Every 8 hours	3 hours
<b>Patients with impaired renal function</b>			
Mild renal impairment (CrCl 60 to < 90 mL/min)	2 g	Every 8 hours	3 hours
Moderate renal impairment (CrCl 30 to < 60 mL/min)	1.5 g	Every 8 hours	3 hours
Severe renal impairment (CrCl 15 to < 30 mL/min)	1 g	Every 8 hours	3 hours
ESRD (CrCl < 15 mL/min)	0.75 g	Every 12 hours	3 hours
Patient with intermittent HD <sup>a</sup>	0.75 g	Every 12 hours	3 hours
Patient with CVVH	1 g	Every 12 hours	3 hours
Patient with CVVHD or CVVHDF	1.5 g	Every 12 hours	3 hours
<b>Patients with augmented renal function</b>			
Augmented renal clearance (CrCl ≥ 120 mL/min)	2 g	Every 6 hours	3 hours

CFDC, cefiderocol; CrCl, creatinine clearance estimated by Cockcroft-Gault equation; CVVH, continuous venovenous hemofiltration; CVVHD, continuous venovenous HD; CVVHDF, continuous venovenous hemodiafiltration; ESRD, end-stage renal disease; HD, hemodialysis.

a. CFDC is hemodialyzable; thus, administer CFDC at the earliest possible time after HD on HD days.

## 8.4 Clinical Pharmacology Conclusions

Six clinical pharmacology studies were conducted to support the limited-use indication of cefiderocol. The PK of cefiderocol is predictable. The  $C_{max}$  and AUC of cefiderocol increased in proportion to the dose. After multiple-dose administration of cefiderocol to healthy adults with normal renal function, slight accumulation of cefiderocol was observed at doses ≤ 2 g administered q8h for 10 days. More than 90% of cefiderocol is eliminated in the urine in an unchanged form. No clinically meaningful effect on PK of age, sex, body weight, or race was observed in the clinical pharmacology studies. No QT prolongation or drug-drug interaction was demonstrated.

For maximum duration of plasma drug exposure against highly resistant pathogens, the recommended dose of cefiderocol is 2 g q8h with a 3-hour infusion in patients with

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normal renal function. Dose adjustment is required for patients with renal impairment and for those with ARC.

## 9 cUTI STUDY

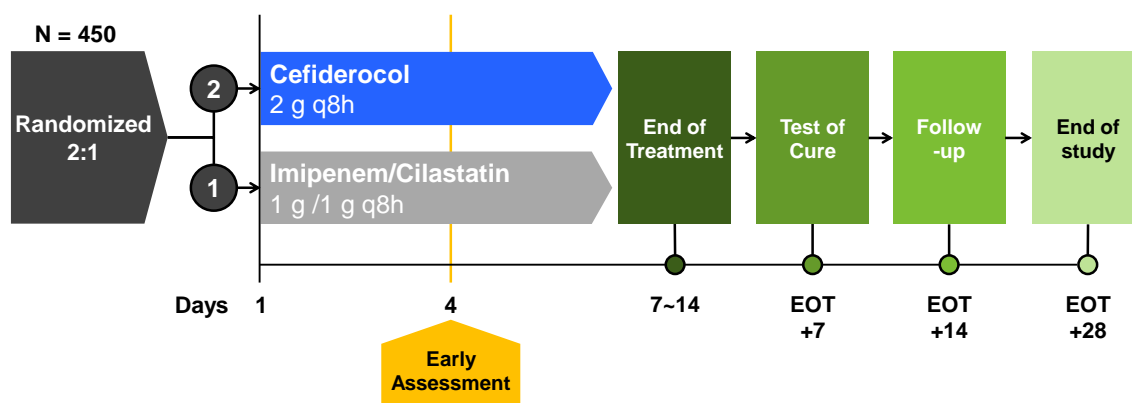
The clinical efficacy and safety profile of cefiderocol was established in the pivotal study investigating the treatment of cefiderocol in cUTI, including pyelonephritis.

The cUTI study included hospitalized patients with carbapenem-susceptible Gram-negative bacteria but aimed to include patients who were at risk for MDR infections originating from cUTI. There was no option to switch to oral therapy; therefore, these patients were likely to require 7 to 14 days of IV antibiotic therapy. Use of IPM/CS, a carbapenem, as the active control precluded enrollment of patients known to be infected with CR pathogens, but enabled enrollment of patients with *Pseudomonas* infection, including those who might have had sepsis.

### 9.1 cUTI Study Design

The cUTI study was a Phase 2, multicenter, multinational, double-blind, randomized, active-controlled, parallel-group study in patients diagnosed with cUTI with or without pyelonephritis or acute uncomplicated pyelonephritis (AUP) (Figure 16). Randomization was stratified according to the patient's clinical diagnosis, (cUTI with or without pyelonephritis and AUP) and region (North America, European Union, Russia, and Japan plus the rest of world).

**Figure 16** cUTI Study Design



cUTI, complicated urinary tract infection; EOT, end of treatment; q8h, every 8 hours.

Eligible participants were hospitalized patients  $\geq 18$  years of age who met the FDA diagnostic criteria for cUTI (draft FDA 2012, finalized FDA 2015, the study was completed prior to a June 2018 revision): clinical syndrome characterized by pyuria and a documented or suspected microbial pathogen on culture of urine or blood, accompanied by local and systemic signs and symptoms, including fever ( $\geq 38^{\circ}\text{C}$ ), chills, malaise, flank pain, back pain, or costovertebral angle pain or tenderness that occurred in the presence of a functional or anatomical abnormality of the urinary tract or in the presence of catheterization and required IV treatment.

Patients with AUP are generally healthy and have infections caused by broadly susceptible bacteria. To ensure enrollment of sicker, more complicated, and difficult to treat patients, the study limited the proportion of patients with AUP to 30%, prohibited switching to oral therapy, and eliminated some exclusion criteria to allow inclusion patients with comorbid conditions, who would be more likely to have MDR pathogens causing their cUTI. This study also permitted those with moderate to severe renal insufficiency to participate, provided their CrCl was  $\geq 21$  mL/min.

Disease severity (mild, moderate, or severe) was determined by the investigator's clinical judgment. Patients with a baseline urine culture with  $> 2$  uropathogens, a fungal UTI, or pathogens known to be carbapenem (imipenem) resistant were excluded from enrollment. Patients receiving hemodialysis or peritoneal dialysis and patients with CrCl of  $< 21$  mL/min were also excluded because no dosing recommendations were available for patients with end-stage renal disease (ESRD) at the time of the study.

Patients received 1-hour IV infusions of either cefiderocol 2 g or IPM/CS 1 g /1 g q8h for a recommended treatment duration of 7 to 14 days (with an option to stop after 5 days if clinically indicated), with dose adjustment for reduced renal function, bodyweight, or both. The high dose of 1 g/1 g per day of IPM/CS was selected to allow the inclusion of patients with infections caused by non-fermenting Gram-negative bacteria such as *P. aeruginosa*, in addition to Enterobacteriaceae. Sequential oral antibiotic (step-down) therapy was not permitted.

## 9.2 Efficacy Endpoints

The primary efficacy endpoint was the composite of clinical and microbiological response at the test of cure (TOC) assessment, defined as 7 days ( $\pm 2$  days) after the end of antibiotic treatment. Clinical response was defined as resolution or improvement of baseline clinical signs and symptoms of cUTI, and no new symptoms of cUTI as assessed by the investigator. Microbiological response was defined as a urine culture that showed the bacterial uropathogen(s) found at baseline that were  $\geq 10^5$  colony forming units (CFU)/mL are reduced to  $< 10^4$  CFU/mL). Primary efficacy analyses were done in the microbiological intent-to-treat (mITT) population, which included all randomly assigned patients who received at least 1 dose of study drug and had a qualifying Gram-negative uropathogen ( $\geq 10^5$  CFU/mL). Analysis of the composite response rate at TOC in the Microbiologically Evaluable (ME) population served as a sensitivity analysis for the primary efficacy endpoint. The ME population included patients in the mITT population who met the evaluation criteria of 5 to 14 days of IV therapy unless patient was a failure, available TOC assessment  $7 \pm 2$  days after end of treatment (EOT) unless patient was assessed a failure earlier, no major protocol inclusion or exclusion violations, no violations of restrictions for concomitant antibiotics effective against Gram-negative bacteria before TOC, no violation of coadministration of valproic acid, probenecid, methotrexate, or procainamide before EOT, and a culture available at both baseline and TOC.

Noninferiority of cefiderocol to IMP/CS for the primary efficacy analysis was to be concluded if the lower bound of a 2-sided 95% CI for the difference between the two

treatment groups was greater than -15 % as discussed with the FDA and outlined in the guidance discussing streamlined development for cUTI indications (FDA draft 2013, final 2017). The adjusted treatment difference estimates and 95% CIs for the noninferiority analysis were calculated using a stratified analysis with Cochran-Mantel-Haenszel weights based on the stratification factor at baseline (cUTI with or without pyelonephritis vs. AUP). In addition, a post-hoc test for superiority was conducted using the adjusted difference and the standard error with Cochran-Mantel-Haenszel weights based on the stratification factor at baseline.

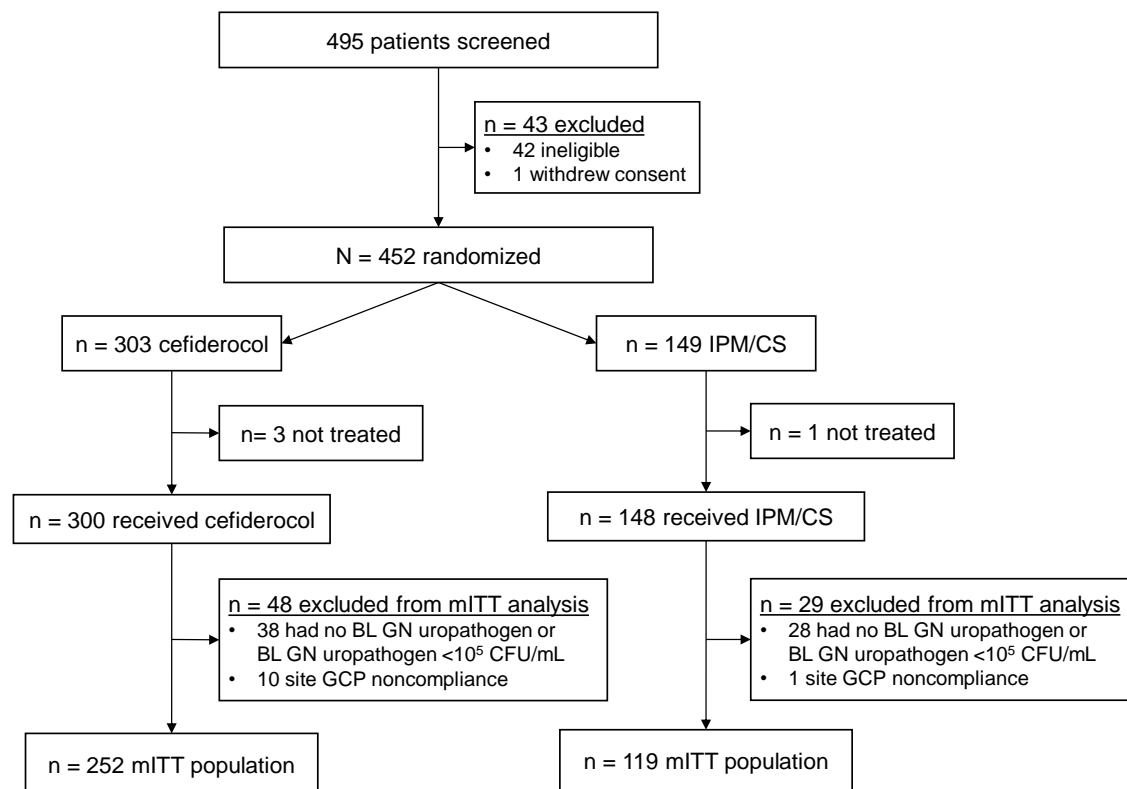
Secondary endpoints were safety, clinical and microbiological response at early assessment (EA, day 4  $\pm$  1 day), last day of study drug/ EOT, and follow-up (FU) approximately 14 days after EOT, and microbiological and clinical response per-pathogen and per-patient at EA, EOT, TOC, and FU. Clinical outcome was based on the investigator's evaluation of patient's clinical signs and symptoms, with response defined as resolution or improvement of cUTI symptoms present at study entry and the absence of new symptoms. Physician assessment was supported by an iterative structured patient interview, which was used for sensitivity analyses of clinical and composite response at TOC. Microbiological outcome was based on quantitative microbiological urine cultures, with response defined as  $< 10^4$  CFU/mL. A central reference laboratory (JMI Laboratories, North Liberty, IA, USA) confirmed the isolate identification and performed antimicrobial susceptibility testing against a panel of antibiotics, including cefiderocol. In addition, they performed molecular analysis for ESBL and carbapenemase resistance genes.

### 9.3 Study Disposition

Overall, 452 patients were randomly allocated (2:1 randomization) to receive cefiderocol (n = 303) or IPM/CS (n = 149), of whom 448 received treatment (the Safety Population: n = 300 cefiderocol group, n = 148 IPM/CS group; [Figure 17](#)). The mITT population included 371 patients (n = 252 cefiderocol group, n = 119 IPM/CS group) with a qualifying Gram-negative uropathogen ( $\geq 10^5$  CFU/mL).

Completion of treatment was defined as treatment cure/patient recovery or achieving  $\geq 5$  days of study treatment. A total of 437 patients (96.7%) completed treatment: 96.7% of patients in the cefiderocol group and 96.6% of patients in the IPM/CS group. Patients could have completed treatment and still discontinued prematurely from the study by not completing all follow-up visits. A total of 421 patients completed the study: 93.4% of patients in the cefiderocol group and 92.6% (138/149) of patients in the IPM/CS group. The most frequent reasons for discontinuing from the study were "lost to follow-up" and "withdrawal by patient".

**Figure 17 cUTI Study Disposition**



BL, baseline; CFU, colony forming unit; GN, Gram-negative; IPM/CS, imipenem/cilastatin; mITT, microbiological intent to treat.

## 9.4 Demographic and Baseline Characteristics

Demographic and baseline characteristics were similar between the treatment groups (Table 12). The majority of patients were enrolled from European study sites resulting in the preponderance of White patients. The proportion of patients with acute uncomplicated pyelonephritis (AUP) was 26% in the cefiderocol group and 29% in the IPM/CS group, which might be a result of more men (47.2 % vs. 40.3 %) in the cefiderocol group than in the IPM/CS group, respectively. In each treatment group, 55% of patients were  $\geq 65$  years of age and 24% of patients were  $\geq 75$  years of age.

**Table 12**                      **Demographics and Baseline Characteristics in the cUTI Study (mITT)**

Parameter		CFDC n = 252	IPM/CS n = 119
Sex, n (%)	Men	119 (47)	48 (40)
	Women	133 (53)	71 (60)
Age, y	Mean ± SD	62.3 ± 16.10	61.3 ± 18.48
	≥ 65, n (%)	139 (55)	65 (55)
	≥ 75, n (%)	61 (24)	29 (24)
Race, n (%)	White	241 (96)	115 (97)
	Black/African American	1 (< 1)	0
	Asian	9 (4)	4 (3)
	Native Hawaiian/Pacific Islander	1 (< 1)	0
BMI	Mean ± SD	27.60 ± 4.9	26.98 ± 6.8
Creatinine clearance renal grading group <sup>a</sup> , n (%)	> 50 to 80 (mild)	78 (31)	41 (34)
	30 to 50 (moderate)	41 (16)	23 (19)
	< 30 (severe)	7 (3)	4 (3)
Baseline clinical diagnosis, n (%)	cUTI with or without pyelonephritis	187 (74)	84 (71)
	cUTI with pyelonephritis	65 (26)	29 (24)
	cUTI without pyelonephritis	122 (48)	55 (46)
	AUP	65 (26)	35 (29)
	Any pyelonephritis	130 (52)	64 (54)
Disease severity, n (%)	Mild	26 (10)	11 (9)
	Moderate	176 (70)	88 (74)
	Severe	50 (20)	20 (17)
Medical history associated with renal stones <sup>b</sup> , n (%)	No	189 (75)	81 (68)
	Yes	63 (25)	38 (32)
Previous infection history <sup>c</sup> , n (%)	No	147 (58)	74 (62)
	Yes	105 (42)	45 (38)
	cUTI	79 (31)	32 (27)
	Other infection	32 (13)	15 (13)
Previous antimicrobial medication status <sup>d</sup> , n (%)	No	229 (91)	107 (90)
	Yes	23 (9)	12 (10)
	Treatment of UTI	17 (7)	11 (9)
	Prophylaxis for UTI	4 (2)	2 (2)
	Treatment of other infection	3 (1)	0
	Surgical prophylaxis	0	0

Parameter		CFDC n = 252	IPM/CS n = 119
Number of baseline antimicrobial- agents, pathogen was resistant to <sup>e</sup> , n (%)	0	117 (46)	60 (50)
	1	58 (23)	27 (23)
	3	13 (5)	4 (3)
	4	5 (2)	2 (2)
	ND	20 (8)	7 (6)
Indwelling urinary catheter <sup>f</sup> , n (%)	No	207 (82)	102 (86)
	Yes	45 (18)	17 (14)
Obstructive uropathy <sup>g</sup> , n (%)	No	167 (66)	81 (68)
	Yes	85 (34)	38 (32)
Number of Gram-negative uropathogens $\geq 10^5$ CFU/mL isolated at baseline, n (%)	1	241 (96)	115 (97)
	2	11 (4)	4 (3)
Number of Gram-negative pathogens isolated from both <sup>h</sup> urine ( $> 10^5$ CFU/mL) and blood cultures at baseline, n (%)	0	234 (93)	111 (93)
	1	18 (7)	8 (7)

AUP, acute uncomplicated pyelonephritis; BMI, body-mass index; CFDC, cefiderocol; cUTI, complicated urinary tract infection; IPM, imipenem; IPM/CS, imipenem/cilastatin; mITT, microbiological intent to treat; ND, not done; SD, standard deviation; UTI, urinary tract infection.

a. Creatinine clearance was calculated using the Cockcroft-Gault formula

$$([140 - \text{age in years}] \times [\text{weight in kg}]) / (72 \times \text{serum creatinine in mg/dL [multiplied by 0.85 for women]})$$
using data from the central laboratory.

b. Medical history associated with renal stones includes nephrolithiasis, calculus bladder, ureterolithiasis, or calculus urinary.

c. Previous history of a cUTI or history of previous infections requiring antimicrobial treatment within the last 12 months.

d. Previous antimicrobial therapy taken 2 weeks before randomization for cUTI or other infections.

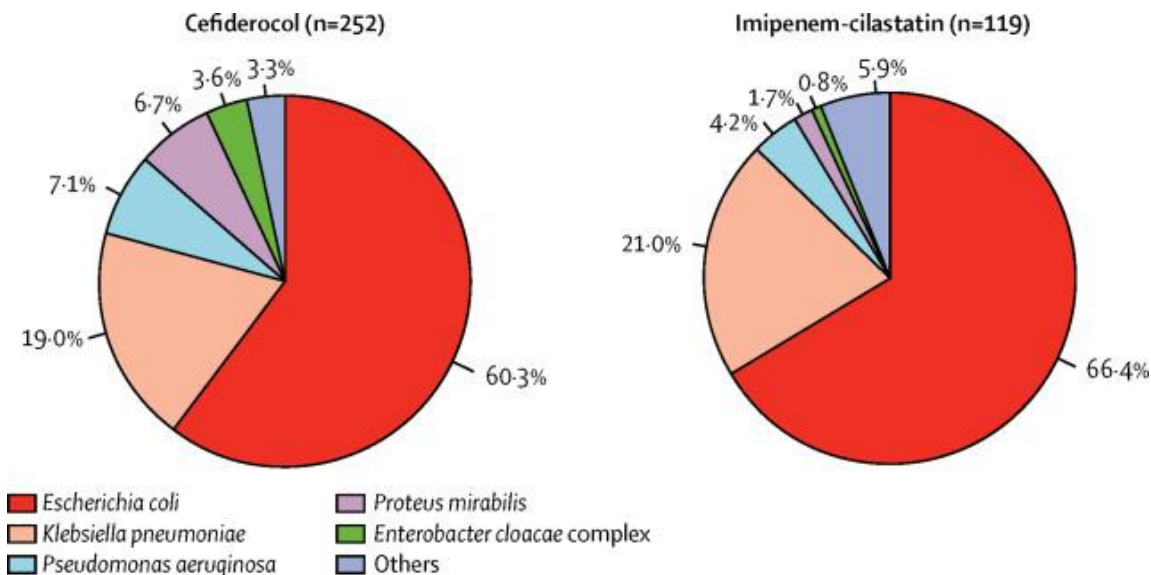
e. MDR is defined as resistance to  $\geq 3$  classes of antibiotics. Antimicrobials tested included IPM, cefepime, piperacillin-tazobactam, and levofloxacin. If a patient had multiple Gram-negative pathogens at baseline, the maximum number of baseline resistant antimicrobials was used. f. Indwelling urinary catheter or instrumentation of the urinary tract within 14 days before screening.

g. Obstructive uropathy such as nephrolithiasis or fibrosis.

h. Previous antimicrobial therapy taken 2 weeks before randomization for cUTI or other infections.

The most prevalent baseline Gram-negative uropathogens isolated from patients were *E. coli* and *K. pneumoniae* (Figure 18). The proportions of patients infected with *E. coli* and *K. pneumoniae* were similar in the cefiderocol and IPM/CS groups. *P. aeruginosa* was more prevalent at baseline in the cefiderocol group than in the IPM/CS group.

**Figure 18**                      **Distribution of Gram-Negative Uropathogens Isolated at Baseline in the cUTI Study (mITT)**



mITT, microbiological intent to treat.

Phenotypic susceptibility of pathogens isolated before treatment was tested by the central lab (JMI, Iowa USA). In the cefiderocol group, 24/45 (53%) of *K. pneumoniae* isolates were resistant to cefepime and levofloxacin, 55/143 (38%) of *E. coli* isolates were levofloxacin resistant, and 24/143 (17%) of *E. coli* isolates were cefepime resistant. In the IPM/CS group, 13/23 (57%) of *K. pneumoniae* isolates were resistant to cefepime, 10/23 (44%) of *K. pneumoniae* isolates were resistant to levofloxacin, 12/76 (16%) *E. coli* isolates were cefepime resistant, and 28 (37%) *E. coli* isolates were levofloxacin resistant. IPM resistance was observed in 5/45 (11%) of *K. pneumoniae* isolates in the cefiderocol group compared with 1/23 (4%) isolates in the IPM/CS group. No cefiderocol isolates had an MIC  $\geq 4$ .

The median ( $\pm$  SD) duration of treatment in the mITT population was  $9.0 \pm 2.7$  days for the cefiderocol group and  $9.0 \pm 2.6$  days for the IPM/CS group.

## 9.5 cUTI Efficacy Results

### 9.5.1 Primary Endpoint Analysis

Cefiderocol met the requirements for noninferiority for the primary endpoint, which was the composite of microbiological eradication and clinical response at TOC. The primary endpoint was achieved by 72.6% of patients in the cefiderocol group and 54.6% of patients in the IPM/CS group, with an adjusted treatment difference of 18.6% (95% CI: 8.2%, 28.9%) in favor of cefiderocol (Figure 19). This result met the criterion for noninferiority at the prespecified -15% margin. A post-hoc superiority analysis yielding a lower limit of the confidence interval of 8.2%, exceeding zero, shows the robustness of the result of cefiderocol compared with IPM/CS.

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## **9.5.2 Secondary Endpoint Outcome Analyses**

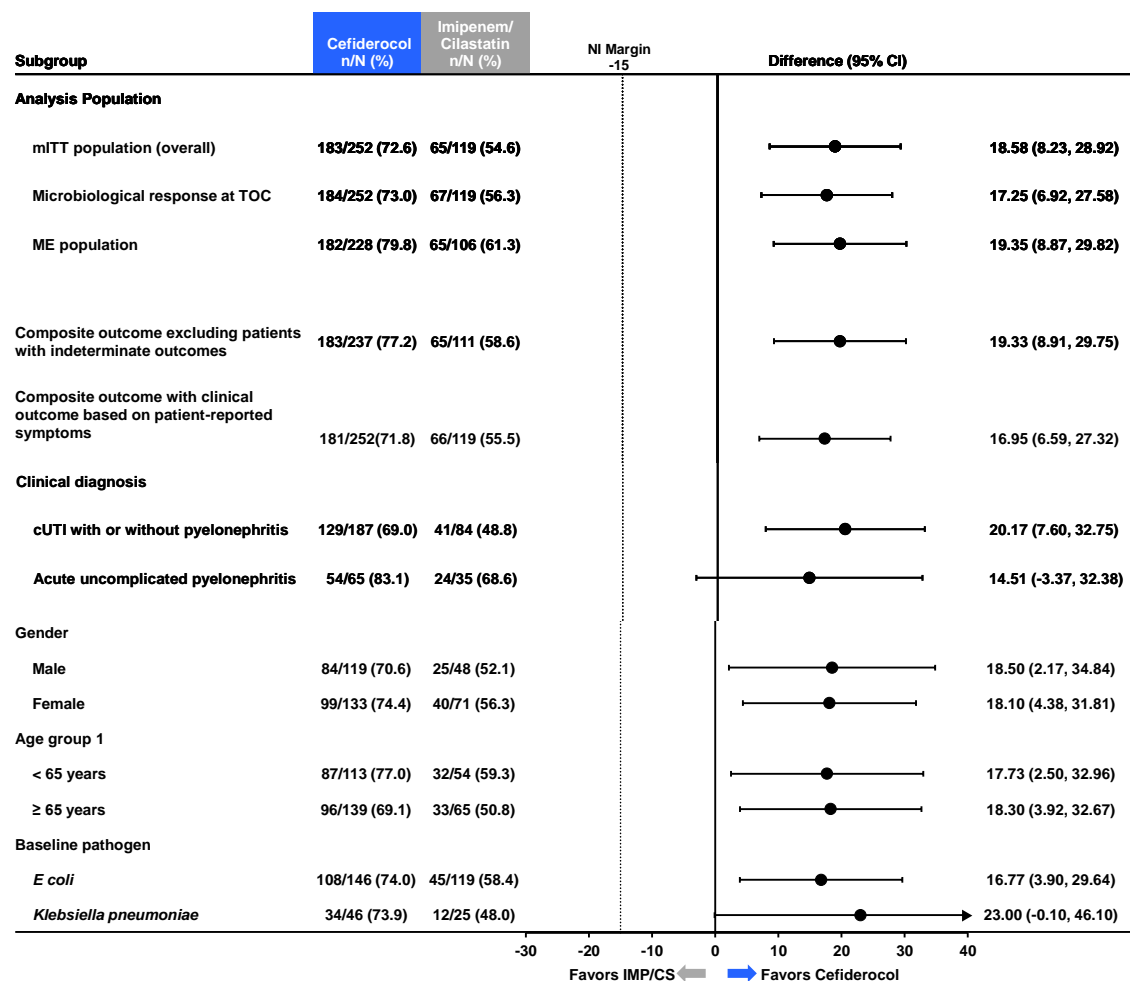
### **9.5.2.1 Response Rate in the ME Population**

The response rate for the primary endpoint at TOC in the ME population was 79.8% of patients in the cefiderocol group and 61.3% of patients in the IPM/CS group, with an adjusted treatment difference of 19.3% (95% CI: 8.87, 29.82) in favor of cefiderocol (Figure 19). These results again are consistent with the primary endpoint conclusion of noninferiority of cefiderocol to IPM/CS with the prespecified -15% margin. Also, consistent with the primary endpoint result, the lower limit of the 95% CI for the between-group difference exceeded 0, again demonstrating the robustness of cefiderocol over IPM/CS.

### **9.5.2.2 Response Rate in Sensitivity Analyses and Subgroups**

Supporting the results of the primary endpoint analysis, sensitivity analyses including analysis in different populations and predefined subgroup analyses (ie, clinical diagnosis, gender, age, baseline pathogen) displayed similar treatment effects across the analyses (Figure 19). The mITT population was mainly White (96%), and therefore, a subgroup analysis by race would not be meaningful.

**Figure 19 Outcomes at Test of Cure for Primary Endpoint, Sensitivity Analyses, and Subgroups**



infection; mITT, microbiological intent-to-treat; NI, noninferiority. Dotted line represents the prespecified non-inferiority margins at -15 %. Treatment difference was adjusted for stratification factors at baseline (cUTI with or without pyelonephritis vs. acute uncomplicated pyelonephritis and region).

An additional sensitivity analysis was conducted that excluded all patients with an indeterminate response at TOC. The response rate for the primary endpoint at TOC in the analysis excluding patients with an indeterminate outcome was 77.2% of patients in the cefiderocol group and 61.3% of patients in the IPM/CS group, with an adjusted treatment difference of 19.3% (95% CI: 8.91, 29.75). This sensitivity analysis was consistent with the primary response and favored cefiderocol. A further post-hoc sensitivity analysis imputing worse case results for indeterminate responses was performed when patients with indeterminate responses in the cefiderocol group (15/252 [6.0%]) are considered failures and patients with indeterminate responses in the IPM/CS group (8/119 [6.7%]) are considered responders. The response rate with this imputation for cefiderocol is 72.6% compared with 61.3% for IPM/CS. The adjusted treatment

difference of 11.8% remains consistent with the overall result of noninferiority at the -15% margin, with the lower bound of the 95% CI at 1.64.

#### **9.5.2.3 Response Rate by Time Point**

The response rates by time point for the mITT population are presented in [Table 13](#). At TOC, the proportion of patients who had a microbiological response was 73% in the cefiderocol group and 56% in the IPM/CS group, whereas the proportion of patients who had a clinical response was 90% in the cefiderocol group and 87% in the IPM/CS group. Notably, although initially similar, the difference between treatment groups begins to favor cefiderocol at TOC through FU for clinical outcome.

**Table 13 Summary of Outcomes by Time Point (mITT)**

Time Point	Outcome	CFDC n = 252 n (%)	IPM/CS n = 119 n (%)	Treatment Difference, % (95 % CI)
<b>Composite clinical and microbiological outcome</b>				
EA	Response	222 (88.1)	104 (87.4)	0.7 (-6.5, 7.8)
	Failure	24 (9.5)	11 (9.2)	-
	Indeterminate	6 (2.4)	4 (3.4)	-
EOT	Response	243 (96.4)	114 (95.8)	0.7 (-3.5, 4.9)
	Failure	5 (2.0)	3 (2.5)	-
	Indeterminate	4 (1.6)	2 (1.7)	-
TOC	Response	183 (72.6)	65 (54.6)	18.6 (8.2, 28.9)
	Failure	54 (21.4)	46 (38.7)	-
	Indeterminate	15 (6.0)	8 (6.7)	-
FU	Response	137 (54.4)	47 (39.5)	15.3 (4.7, 25.9)
	Failure	92 (36.5)	49 (41.2)	-
	Indeterminate	23 (9.1)	23 (19.3)	-
<b>Microbiological outcome</b>				
EA	Microbiological eradication	232 (92.1)	108 (90.8)	1.3 (-4.8, 7.4)
	Microbiological persistence	14 (5.6)	7 (5.9)	-
	Indeterminate	6 (2.4)	4 (3.4)	-
EOT	Microbiological eradication	244 (96.8)	114 (95.8)	1.1 (-3.0, 5.3)
	Microbiological persistence	3 (1.2)	3 (2.5)	-
	Indeterminate	5 (2.0)	2 (1.7)	-
TOC	Microbiological eradication	184 (73.0)	67 (56.3)	17.3 (6.9, 27.6)
	Microbiological persistence	53 (21.0)	44 (37.0)	-
	Indeterminate	15 (6.0)	8 (6.7)	-
FU	Sustained microbiological eradication	144 (57.1)	52 (43.7)	13.9 (3.2, 24.6)
	Microbiological persistence or recurrence	84 (33.3)	42 (35.3)	-
	Indeterminate	24 (9.5)	25 (21.1)	-
<b>Clinical outcome</b>				
EA	Clinical response	228 (90.5)	108 (90.8)	-0.3 (-6.8, 6.1)
	Clinical failure	23 (9.1)	10 (8.4)	-
	Indeterminate	1 (0.4)	1 (0.8)	-
EOT	Clinical response	247 (98.0)	118 (99.2)	-1.1 (-3.4, 1.3)
	Clinical failure	4 (1.6)	0	-
	Indeterminate	1 (0.4)	1 (0.8)	-
TOC	Clinical response	226 (89.7)	104 (87.4)	2.4 (-4.7, 9.4)
	Clinical failure	14 (5.6)	8 (6.7)	-
	Indeterminate	12 (4.8)	7 (5.9)	-
FU	Sustained clinical response	205 (81.3)	86 (72.3)	9.0 (-0.4, 18.4)
	Clinical failure	19 (7.5)	13 (10.9)	-
	Clinical relapse	12 (4.8)	12 (10.1)	-
	Indeterminate	16 (6.3)	8 (6.7)	-

CFDC, cefiderocol; EA, early assessment; EOT, end of treatment; FU, follow-up; IPM/CS, imipenem/cilastatin; TOC, test of cure.

#### 9.5.2.4 Per-Pathogen Analyses

The treatment differences in the composite response at TOC for patients with *E. coli* (108/146 [74.0%] cefiderocol patients vs. 45/77 [58.4%] IPM/CS patients) and *K. pneumoniae* (34/46 [73.9%] cefiderocol patients vs. 12/25 [48.0%] IPM/CS patients) infection favored cefiderocol and were consistent with the primary analysis. Other uropathogens were less prevalent, below 10 in either group, making comparison to the primary analysis difficult. At TOC, the proportion of patients who met the composite outcome for *P. aeruginosa* was similar between treatment groups (7/15 [46.7%] cefiderocol patients vs. 2/4 [50.0%] IPM/CS patients) and lower than the overall response rate. Extended-spectrum  $\beta$ -lactamase producing Gram-negative uropathogens were identified by next-generation sequencing. The proportion of patients who had a composite response for extended-spectrum  $\beta$ -lactamase-producing baseline Gram-negative uropathogens (44/70 [62.9%] cefiderocol patients vs. 17/36 [47.2%] IPM/CS patients) and was consistent with the primary analysis.

#### 9.5.2.5 Analysis of Clinical Outcome by Patient-Reported Symptoms

The clinical outcome based on patient-reported symptoms serves as a comparative analysis for the physician-assessed clinical response. Patient-reported symptoms were collected using a Structured Patient Interview that assessed resolution of all the core symptoms of cUTI (dysuria, urinary frequency, urinary urgency, suprapubic pain, and flank pain). Baseline symptoms associated with anatomic abnormalities that predispose to cUTI, such as symptoms associated with the presence of an indwelling urinary catheter, did not need to be resolved for a consideration of successful responder. Clinical response at TOC was reported in 226/252 (89.7%) patients in the cefiderocol group compared with 101/119 (84.9%) patients in the IPM/CS group, consistent with the clinical response rates reported by the investigators, (89.7% and 87.4% for cefiderocol and IPM/CS, respectively) providing support and internal validation for the physician-assessed clinical response.

#### 9.5.3 Efficacy Conclusions of the cUTI Study

The cUTI study demonstrated that in a hospitalized population of 448 patients, with multiple comorbidities and difficult-to-treat infections, cefiderocol was noninferior to a standard-of-care antibiotic comparator, IPM/CS. Although the study was only designed to demonstrate noninferiority, the findings of a post-hoc analysis were consistent with superiority. The adjusted treatment difference favored cefiderocol and the lower limit of the 95 % confidence interval exceeded 0. The absolute difference of 18.58% in the composite primary endpoint was supported across all analyzed populations and clinical diagnostic groups with cUTI. The magnitude of the observed treatment differences is considered clinically important. Sensitivity analyses also showed that cefiderocol had better microbiological efficacy than IPM/CS in predefined subgroups and in patients infected with *E. coli* and *K. pneumoniae*, the most prevalent uropathogens.

## 9.6 cUTI Safety Findings

Based on the results of this study, the safety profile of cefiderocol is well characterized and supports its use for the treatment of cUTI. The rates, types, and severity of AEs were predictable for a cephalosporin, and cefiderocol was generally well tolerated.

### 9.6.1 Exposure

The Safety Population in the cUTI study included 448 patients who received at least one dose of study treatment, with 300 patients in the cefiderocol group and 148 patients in the IPM/CS group. The mean ( $\pm$  SD) duration of treatment in the safety population was  $9.4 \pm 2.7$  days for the cefiderocol group and  $9.5 \pm 2.6$  days for the IPM/CS group (Table 14). The median duration was 9 days in both treatment arms. Over 90% of patients in both treatment groups received from 7 to 14 days of treatment. Only 2.7% of patients in each treatment group were exposed to less than 5 days of study treatment. A similar proportion of patients in each group had protocol-recommended dose changes or adjustments for weight or renal function reasons.

**Table 14 Duration of Exposure (Safety Population)**

Parameter Statistic/Category	Cefiderocol n = 300	IPM/CS n = 148
<b>Duration of exposure, days<sup>a</sup></b>		
Mean $\pm$ SD	$9.4 \pm 2.69$	$9.5 \pm 2.62$
Median (min, max)	9.0 (1, 15)	9.0 (2, 15)
<b>Duration of exposure category, n (%)</b>		
< 5 days	8 (2.7)	4 (2.7)
5 to < 7 days	10 (3.3)	1 (0.7)
7 to $\leq$ 14 days	277 (92.3)	141 (95.3)
> 14 days	5 (1.7)	2 (1.4)
<b>Dosing status, n (%)</b>		
Patients who had an infusion interruption	6 (2.0)	2 (1.4)
<b>Dose change/adjustment, n (%)</b>		
Yes	52 (17.3)	27 (18.2)

CFDC, cefiderocol; IPM/CS, imipenem/cilastatin; SD, standard deviation.

a. Duration of exposure to study drug (days) = last dose date of study drug – 1<sup>st</sup> dose date of study drug + 1.

### 9.6.2 Patient Disposition

The proportions of patients who received study treatment, completed treatment, and completed the study were high and similar between the treatment groups (Table 15). Most patients in both treatment groups received  $\geq 1$  dose of study drug, and most completed the study. The most frequent reason for discontinuation was “lost to follow-up”. The percentage of AEs resulting in discontinuation in the cefiderocol group was 0.7%, and 2.0% in the IPM/CS group. One patient who received cefiderocol died during the study (See Section 9.6.4.1, below). The death was considered unrelated to study drug.

**Table 15 Patient Disposition (All Randomized Patients)**

	<b>Cefiderocol n (%)</b>	<b>IPM/CS n (%)</b>
Patients Randomized	303 (100.0)	149 (100.0)
Patients not treated	3 (1.0)	1 (0.7)
Patients treated	300 (99.0)	148 (99.3)
<b>Study status:</b>		
Completed the study <sup>a</sup>	283 (93.4)	138 (92.6)
Discontinued from the study	20 (6.6)	11 (7.4)
Withdrawal by patient	3 (1.0)	3 (2.0)
Death	1 (0.3)	0
Protocol Violation	1 (0.3)	0
Lost to Follow-up	10 (3.3)	4 (2.7)
AE	2 (0.7)	3 (2.0)
Other	3 (1.0)	1 (0.7)

CFDC, cefiderocol; IPM/CS, imipenem/cilastatin.

a. Completed the study including all follow-up visits.

Percentage is calculated using the number of randomized patients as the denominator.

### 9.6.3 Baseline Characteristics and Demographics in the Safety Population

The mean age of the Safety Population was 61.2 years; 52.7% of patients were 65 or over years of age, 22.8% were  $\geq 75$  years, and 2.7% were  $\geq 85$  years of age (Table 16). Most patients were female (54.7%), White (95.8%), and non-Hispanic (98.4%). No meaningful differences were observed in demographic characteristics between the cefiderocol and IPM/CS treatment groups.

**Table 16**                      **Demographics and Baseline Characteristics in the cUTI Study (Safety Population)**

Parameter		Cefiderocol n = 252	IPM/CS n = 119
Sex, n (%)	Men	137 (45.7)	66 (44.6)
	Women	163 (54.3)	82 (55.4)
Age, y	Mean ± SD	61.1 ± 16.5	61.3 ± 17.8
	≥ 65, n (%)	158 (52.7)	78 (52.7)
	≥ 75, n (%)	67 (22.3)	35 (23.6)
	≥ 85, n (%)	6 (2.0)	6 (4.1)
Duration of cUTI diagnosis prior to randomization, days	Mean ± SD	2.2 ± 4.5	2.4 ± 3.7
	Median (min, max)	1.0 (1, 67)	2.0 (1, 32)
Creatinine clearance renal grading group <sup>a</sup> , n (%)	> 80 (normal)	152 (50.7)	63 (42.6)
	> 50 to 80 (mild)	89 (29.7)	50 (33.8)
	30 to 50 (moderate)	49 (16.3)	28 (18.9)
	< 30 (severe)	8 (2.7)	7 (4.7)
Disease severity, n (%)	Mild	33 (11.0)	11 (7.4)
	Moderate	208 (69.3)	112 (75.7)
	Severe	59 (19.7)	25 (16.9)
Medical history associated with renal stones <sup>b</sup> , n (%)	No	230 (76.7)	101 (68.2)
	Yes	70 (23.3)	47 (31.8)
Previous infection history <sup>c</sup> , n (%)	No	176 (58.7)	89 (60.1)
	Yes	124 (41.3)	59 (39.9)
	cUTI	96 (32.0)	43 (29.1)
	Other infection	37 (12.3)	19 (12.8)
Previous antimicrobial medication status <sup>d</sup> , n (%)	No	269 (89.7)	133 (89.9)
	Yes	31 (10.3)	15 (10.1)
	Treatment of UTI	24 (8.0)	14 (9.5)
	Prophylaxis for UTI	6 (2.0)	2 (1.4)
	Treatment of other infection	3 (1.0)	1 (0.7)
	Surgical prophylaxis	0	0
Number of baseline antimicrobial-resistant pathogens <sup>e</sup> , n (%)	0	126 (42.0)	67 (45.3)
	1	63 (21.0)	30 (20.3)
	3	42 (14.0)	20 (13.5)
	4	13 (4.3)	4 (2.7)
	ND	5 (1.7)	2 (1.4)
Indwelling urinary catheter <sup>f</sup> , n (%)	No	251 (83.7)	125 (84.5)
	Yes	49 (16.3)	23 (15.5)
Obstructive uropathy <sup>g</sup> , n (%)	No	196 (65.3)	98 (66.2)
	Yes	104 (34.7)	50 (33.8)

CFDC, cefiderocol; cUTI, complicated urinary tract infection; IPM, imipenem; IPM/CS, imipenem/cilastatin; ND, not done; SD, standard deviation; UTI, urinary tract infection.

a. Creatinine clearance was calculated using the Cockcroft-Gault formula ( $[140 - \text{age in years}] \times [\text{weight}]$

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in kg)]/(72 × serum creatinine in mg/dL [multiplied by 0.85 for women]) using data from the central laboratory.

- b. Medical history associated with renal stones includes nephrolithiasis, calculus bladder, ureterolithiasis, or calculus urinary.
- c. Previous history of a cUTI or history of previous infections requiring antimicrobial treatment within the last 12 months.
- d. Previous antimicrobial therapy taken 2 weeks before randomization for cUTI or other infections.
- e. Number of antimicrobials among IPM, cefepime, piperacillin-tazobactam, and levofloxacin baseline pathogens were resistant to. If a patient had multiple Gram-negative pathogens at baseline, the maximum number of baseline resistant antimicrobials was used. Patients were classified as ND if their baseline pathogens were not analyzed by the central laboratory.
- f. Indwelling urinary catheter or instrumentation of the urinary tract within 14 days before screening.
- g. Obstructive uropathy such as nephrolithiasis or fibrosis.

## 9.6.4 Adverse Events

### 9.6.4.1 Overall Adverse Events

The proportion of any AEs reported in the IPM/CS group was 51.4% (76/148 patients) compared with 40.7% of patients in the cefiderocol group (122/300; [Table 17](#)), and the majority of AEs were mild or moderate in severity. Consistent with the proportion of any AE, a greater proportion of drug-related AEs, serious adverse events (SAEs), and discontinuations due to AEs were reported in the IPM/CS group than in the cefiderocol group.

The only death in the cUTI Study was due to cardiorespiratory arrest in a patient treated with cefiderocol for 6 days and was considered unrelated to study drug by the investigator. The 76-year-old male patient had a normal electrocardiogram (ECG) at Days 1 and 6 with no reported significant abnormalities or QTc prolongation observed. The patient had a complicated medical history that included heart disease, hypertension, hyperlipidemia, diabetes mellitus, cerebral infarction, epilepsy, chronic renal insufficiency, benign prostatic hyperplasia, extrapyramidal disorder, and dementia. This patient entered the study with a cUTI without pyelonephritis and was treated with cefiderocol until Day 7. On Day 7, the patient abruptly experienced cardiorespiratory arrest and died. There had been no subjective complaints or objective clinical finding leading up to this event.

**Table 17 Safety Summary (Safety Population)**

	<b>Cefiderocol n = 300 n (%)</b>	<b>IPM/CS n = 148 n (%)</b>
Any AE	122 (40.7)	76 (51.4)
Mild	77 (25.7)	36 (24.3)
Moderate	39 (13.0)	35 (23.6)
Severe	6 (2.0)	5 (3.4)
Drug-related AE <sup>a</sup>	27 (9.0)	17 (11.5)
SAEs	14 (4.7)	12 (8.1)
Drug-related SAEs	1 (0.3)	1 (0.7)
Discontinuation due to AE <sup>b</sup>	5 (1.7)	3 (2.0)
Discontinuation due to drug-related AEs	3 (1.0)	0
Death <sup>c</sup>	1 (0.3)	0

AE, adverse event; IPM/CS, imipenem/cilastatin; SAE, serious adverse event.

a. Considered treatment related by the investigator.

b. Cefiderocol: *Clostridium difficile*, hypersensitivity (itching), increased hepatic enzymes, diarrhea.

c. Death was not considered to be drug related by the investigator.

For severity, AEs with missing severity data are counted as severe. Patients experiencing > 1 AE are only counted once for the most severe events.

All treatment-emergent AEs that started between the first day of treatment and the end of the study (28 days after last dose of study drug) are included.

#### 9.6.4.2 Common Adverse Events

Gastrointestinal disorders, such as diarrhea and constipation, were the most common AEs; diarrhea was reported in 4.3% patients in the cefiderocol group and 6.1% of patients in the IPM/CS group, and constipation was reported in 3.3% of patients in the cefiderocol group and 4.1% of patients in the IPM/CS group (Table 18).

**Table 18**                      **Adverse Events With Incidence > 2 % in Either Treatment Group (Safety Population)**

<b>AE by Preferred Term</b>	<b>Cefiderocol n = 300 n (%)</b>	<b>IPM/CS n = 148 n (%)</b>
Diarrhea	13 (4.3)	9 (6.1)
Hypertension	13 (4.3)	8 (5.4)
Constipation	10 (3.3)	6 (4.1)
Infusion site pain	9 (3.0)	5 (3.4)
Headache	7 (2.3)	8 (5.4)
Nausea	7 (2.3)	6 (4.1)
Cough	7 (2.3)	1 (0.7)
Vomiting	6 (2.0)	2 (1.4)
Hypokalemia	5 (1.7)	4 (2.7)
Insomnia	4 (1.3)	3 (2.0)
Renal cyst	4 (1.3)	5 (3.4)
Infusion site erythema	3 (1.0)	3 (2.0)
Abdominal pain upper	2 (0.7)	5 (3.4)
Cardiac failure	2 (0.7)	3 (2.0)
<i>Clostridium difficile</i> colitis <sup>a</sup>	1 (0.3)	4 (2.7)
Vaginal infection	1 (0.3)	3 (2.0)

AE, adverse event; IPM/CS, imipenem/cilastatin.

a. An additional AE with the preferred term of *Clostridium difficile* infection was reported in the IPM/CS group.

#### **9.6.4.3 Treatment-Related Adverse Events**

Treatment-related AEs were reported in the cefiderocol group (9.0%) compared with the IPM/CS group (11.5%, [Table 19](#)). No noteworthy differences were found between groups in specific treatment-related AEs.

**Table 19 Treatment-Related Adverse Events by System Organ Class and Preferred Term (Safety Population)**

<b>System Organ Class Preferred Term</b>	<b>Cefiderocol n = 300 n (%)</b>	<b>IPM/CS n = 148 n (%)</b>
Patients with treatment-related AEs	27 (9.0)	17 (11.5)
Cardiac disorders	0	1 (0.7)
Tachycardia	0	1 (0.7)
Gastrointestinal disorders	9 (3.0)	5 (3.4)
Abdominal pain upper	1 (0.3)	0
Constipation	1 (0.3)	0
Diarrhea	4 (1.3)	3 (2.0)
Dry mouth	1 (0.3)	0
Lip edema	0	1 (0.7)
Nausea	3 (1.0)	1 (0.7)
Stomatitis	1 (0.3)	0
Vomiting	1 (0.3)	1 (0.7)
General disorders and administration site conditions	5 (1.7)	0
Feeling hot	1 (0.3)	0
Infusion site erythema	1 (0.3)	0
Infusion site pain	2 (0.7)	0
Edema peripheral	2 (0.7)	0
Hepatobiliary disorders	0	1 (0.7)
Hepatic function abnormal	0	1 (0.7)
Immune system disorders	1 (0.3)	0
Drug hypersensitivity	1 (0.3)	0
Infections and infestations	4 (1.3)	6 (4.1)
Candiduria	2 (0.7)	0
<i>Clostridium difficile</i> colitis	1 (0.3)	4 (2.7)
Fungal infection	0	1 (0.7)
Oral candidiasis	1 (0.3)	0
Vaginal infection	0	1 (0.7)
Investigations	5 (1.7)	2 (1.4)
Alanine aminotransferase increased	1 (0.3)	0
Blood alkaline phosphatase increased	0	1 (0.7)
Blood creatinine increased	0	1 (0.7)
Gamma-glutamyltransferase increased	4 (1.3)	1 (0.7)
Hepatic enzyme increased	1 (0.3)	0
Musculoskeletal and connective tissue disorders	1 (0.3)	0
Myalgia	1 (0.3)	0

System Organ Class Preferred Term	Cefiderocol n = 300 n (%)	IPM/CS n = 148 n (%)
Nervous system disorders	1 (0.3)	4 (2.7)
Dysgeusia	1 (0.3)	1 (0.7)
Headache	0	3 (2.0)
Skin and subcutaneous tissue disorders	3 (1.0)	0
Erythema	1 (0.3)	0
Pruritus	1 (0.3)	0
Rash maculo-papular	1 (0.3)	0

AEs, adverse events; IPM/CS, imipenem/cilastatin; SOC, system organ class.

Percentage is calculated using the number of patients in the column heading as the denominator. All AEs are treatment-emergent that started on or after the first dose date of the study drug and up to 'End of Study' are included. Although a patient may have had 2 or more AEs, the patient is counted only once within an SOC category. The same patient may contribute to 2 or more preferred terms in the same SOC category.

#### 9.6.4.4 Serious Adverse Events

The incidence of SAEs was 4.7% in the cefiderocol group compared with 8.1% in the IPM/CS group (Table 20). All specific SAE Preferred Terms were reported for only 1 or 2 patients in a treatment group and no meaningful differences between groups were observed for any Preferred Term. One SAE of cardio-respiratory arrest in the cefiderocol group was in a patient who later died. As noted above, the investigator determined that the death was not treatment related. The most common SAE was *C. difficile* colitis (1/300 [ $< 1\%$ ] patients in the cefiderocol group vs. 2/148 [1%] patients in the IPM/CS group). The incidence of *C. difficile* colitis in the cefiderocol-treated patient and in 1 of the 2 IPM/CS-treated patients were considered related to treatment by the investigator.

**Table 20**                      **Serious Adverse Events by System Organ Class and Preferred Term (Safety Population)**

<b>System Organ Class Preferred Term</b>	<b>Cefiderocol n = 300 n (%)</b>	<b>IPM/CS n = 148 n (%)</b>
Patients with SAEs	14 (4.7)	12 (8.1)
Blood and lymphatic system disorders	2 (0.7)	0
Anemia	1 (0.3)	0
Hemorrhagic anemia	1 (0.3)	0
Cardiac disorders	3 (1.0)	1 (0.7)
Cardiac failure	1 (0.3)	1 (0.7)
Cardiac failure acute	1 (0.3)	0
Cardio-respiratory arrest	1 (0.3)	0
Myocardial ischemia	1 (0.3)	0
Congenital, familial and genetic disorders	0	1 (0.7)
Congenital ureteric anomaly	0	1 (0.7)
Gastrointestinal disorders	2 (0.7)	2 (1.4)
Diarrhea	1 (0.3)	1 (0.7)
Duodenal ulcer	1 (0.3)	0
Lower gastrointestinal hemorrhage	0	1 (0.7)
Upper gastrointestinal hemorrhage	1 (0.3)	0
General disorders and administration site conditions	1 (0.3)	0
Pyrexia	1 (0.3)	0
Hepatobiliary disorders	1 (0.3)	0
Gallbladder pain	1 (0.3)	0
Infections and infestations	5 (1.7)	6 (4.1)
Abscess	0	1 (0.7)
Ascariasis	1 (0.3)	0
Cellulitis	1 (0.3)	0
<i>Clostridium difficile</i> colitis	1 (0.3)	2 (1.4)
Device related infection	0	1 (0.7)
Pneumonia	1 (0.3)	0
Prostatic abscess	0	1 (0.7)
Pyelonephritis	0	1 (0.7)
Renal abscess	1 (0.3)	0
Urinary tract infection	1 (0.3)	0
Injury, poisoning and procedural complications	0	2 (1.4)
Alcohol poisoning	0	1 (0.7)
Gastrointestinal injury	0	1 (0.7)

<b>System Organ Class Preferred Term</b>	<b>Cefiderocol n = 300 n (%)</b>	<b>IPM/CS n = 148 n (%)</b>
Investigations	1 (0.3)	1 (0.7)
Blood creatine phosphokinase increased	1 (0.3)	0
Hematocrit decreased	0	1 (0.7)
Nervous system disorders	0	1 (0.7)
Ischemic stroke	0	1 (0.7)
Renal and urinary disorders	3 (1.0)	2 (1.4)
Acute kidney injury	0	1 (0.7)
Hydronephrosis	0	1 (0.7)
Obstructive nephropathy	1 (0.3)	0
Ureterolithiasis	1 (0.3)	0
Urinary tract obstruction	1 (0.3)	0
Surgical and medical procedures	1 (0.3)	0
Urethrotomy	1 (0.3)	0
Vascular disorders	0	1 (0.7)
Deep vein thrombosis	0	1 (0.7)

CFDC, cefiderocol; IPM/CS, imipenem/cilastatin; SAEs, serious adverse events, SOC, system organ class.

Percentage is calculated using the number of patients in the column heading as the denominator. All AEs are treatment-emergent that started on or after the first dose date of the study drug and up to 'End of Study' are included. Although a patient may have had 2 or more AEs, the patient is counted only once within an SOC category. The same patient may contribute to 2 or more preferred terms in the same SOC category.

#### 9.6.4.5 Safety in Subgroups

Post-hoc subgroup analyses of AEs in the cUTI study were conducted using the intrinsic factors of age, sex, race, diagnosis (infection type), degree of renal impairment status/dose adjustments, and the extrinsic factor of geographic region. Safety was explored particularly in the vulnerable subgroups of those over 75 years of age and those with renal impairment. Consistent with the overall results, no differences were observed in rates of AEs with increasing age or decreasing renal function, confirming the overall safety of cefiderocol.

#### 9.6.4.6 Adverse Events of Interest

The following adverse events of interest were identified and examined: antibiotic-related AEs of *C. difficile*-related AEs and diarrhea,  $\beta$ -lactam antibiotic class effects of rash/hypersensitivity reactions, liver toxicity and liver failure, seizures/epilepsy, and bone marrow suppression, and issues with iron homeostasis.

#### *C. difficile*-Related Adverse Events and Diarrhea

The incidence of *C. difficile* infection in this study was low. One patient in the cefiderocol group had an AE related to *C. difficile* compared with five patients in the IPM/CS group. The single *C. difficile*-related AE in the cefiderocol group was an SAE of *C. difficile* colitis that was mild in severity and considered related to treatment. In the

IPM/CS group, one patient was reported with a *C. difficile*-related AE (*C. difficile* infection not reported as colitis) that was mild in severity and unrelated to study drug; two patients were reported with *C. difficile* colitis that were moderate in severity and related to study drug, one patient reported two events of *C. difficile* colitis; a moderate in severity event related to study drug and a serious, severe event unrelated to study drug; and one patient was reported with *C. difficile* colitis that was serious, moderate in severity, and related to study drug. All cases of *C. difficile* colitis and *C. difficile* infection in both treatment groups were considered resolved.

Diarrhea as a preferred term was reported in 4.3% (13/300) of patients in the cefiderocol group compared with 6.1% (9/148) of patients in the IPM/CS group. In the cefiderocol group, one diarrhea event was an SAE considered unrelated to study drug and another event of diarrhea was an AE considered related to study drug that led to the withdrawal of study drug. In total, four events of diarrhea were considered related to treatment, and nine events were considered unrelated to treatment. Similarly, nine patients reported events of diarrhea that were mild in severity and four patients reported moderate events.

In the IPM/CS group, one event of diarrhea was an SAE considered unrelated to study drug. Three events of diarrhea were considered related to treatment, and six events, including the SAE, were considered unrelated to treatment. In total, four patients reported events of diarrhea that were mild in severity, and five patients reported moderate events. Diarrhea as a verbatim term with *C. difficile* as a preferred term was reported in an additional two patients in the IPM/CS group. One event was an SAE, and both were moderate in severity and considered related to study drug. In all cases in both treatment groups, the events of diarrhea were considered resolved.

### **Rash and Hypersensitivity**

Rash was reported for 1.7% (5/300) of patients treated with cefiderocol. In addition, macular rash and maculopapular rash were each reported for 1 patient (1/300 [0.3%]) in the cefiderocol group. Overall, with rash, macular rash, and maculopapular rash combined, the incidence was 2.3% (7/300) of patients. Drug hypersensitivity (not associated with rash or systemic symptoms) was reported for one patient treated with cefiderocol who experienced a moderate nonserious AE of drug hypersensitivity, which was limited to itching after the first dose and cefiderocol was discontinued. No patients were reported with anaphylaxis. There were no cases of rash or drug hypersensitivity reported for patients in the IPM/CS group. No SAEs related to rash/hypersensitivity were reported.

### **Liver-Related Adverse Events**

Liver events were defined as meeting the following clinical or biochemical parameters:

- a. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT)  $> 5 \times$  upper limit of normal (ULN)
- b. AST or ALT  $> 3 \times$  ULN and total bilirubin  $> 2 \times$  ULN or prothrombin time (PT) international normalized ratio (INR, [PT-INR])  $> 1.5$ , if PT-INR measured

- c. AST or ALT  $> 3 \times$  ULN with signs or symptoms compatible with hepatitis or hypersensitivity (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, jaundice, fever, rash, or eosinophilia [ $> 5\%$ ])

Liver events were reported for two (0.7%) patients treated with cefiderocol and one (0.7%) patient treated with IPM/CS. No transaminase rises were associated with increases in bilirubin or blood clotting abnormalities. No cases of Hy's law or drug-induced liver injury were observed in the cUTI study.

### **Seizures/Epilepsy**

One cefiderocol recipient with a history of epilepsy had a single seizure that occurred on treatment Day 7; treatment was completed uneventfully for a further 3 days. No evidence of de novo seizure was associated with cefiderocol.

### **Bone Marrow Suppression**

No unexplained anemia or laboratory AEs suggesting bone marrow suppression were observed in this study.

### **Potential Effect of Cefiderocol on Iron Metabolism**

Due to the ability of cefiderocol's catechol moiety to complex with free ferric iron, exploratory investigations (lab tests) of transferrin saturation, total iron binding capacity, hemoglobin, hematocrit, and hepcidin (an iron regulatory hormone) were conducted; no apparent differences between treatment groups for change over time for these parameters were found and no AEs were reported related to iron homeostasis.

## **9.6.5 Resistance to Cefiderocol**

Cultures of post-baseline bacteria showed that in six cases there was a 4-fold increase in MIC to cefiderocol. However, none of these isolates had an MIC  $> 1 \mu\text{g/mL}$ , suggesting that there was no development of resistance to cefiderocol during the study.

## **9.6.6 Safety Conclusions of the cUTI Study**

Cefiderocol was safe and well tolerated in the cUTI study, with an observed safety profile consistent with the cephalosporin class. More than 90% of patients completed treatment in both groups. Between the two treatment groups, AE rates were generally similar.

One case of hypersensitivity, which was limited to itching, was reported in the cefiderocol group. One case of seizure in a patient with epilepsy was reported in the cefiderocol group. No cases of Hy's law or drug-induced liver injury were observed in the cUTI study and no bone marrow suppression or treatment-related thyroid function/abnormalities were reported.

No safety signals were observed that were unique to cefiderocol, including no events associated with iron metabolism and homeostasis. The safety profile of cefiderocol supports its use in cUTI, including use in an elderly population with multiple comorbidities.

## 10 CREDIBLE-CR STUDY

The CREDIBLE-CR study was a randomized, open-label study to assess the efficacy and safety of cefiderocol and best available therapy (BAT) in patients with carbapenem-resistant Gram-negative bacterial infections as the primary objective. A total of 152 patients were randomized to cefiderocol or BAT in a 2 to 1 ratio to obtain qualitative assessments of patients receiving cefiderocol. A total of 150 patients (101 in the cefiderocol group and 49 in the BAT group) received study treatment.

The CREDIBLE-CR study was conceptualized to obtain a general understanding of the efficacy of cefiderocol in infections caused by carbapenem-resistant Gram-negative bacteria, which represent an unmet medical need. Unlike most antibiotic clinical trials, the CREDIBLE-CR study was not limited to a single infection site, but rather included multiple infection sites as long as there was evidence of carbapenem resistance. The study was not designed to provide inferential hypothesis testing but was intended to provide descriptive statistics of the aggregate data. Patient-level information was collected in patient narratives and chronographs. This study is a pivotal study for the European Medicines Agency (EMA) to support a Gram-negative infection indication in Europe.

### 10.1 Study Design

Patients enrolled in the CREDIBLE-CR study have few or no available treatment options because of carbapenem resistance, reflecting real-world care of patients with serious infections and multiple comorbidities. The control arm, BAT, could include one, two or three antibiotics used together whereas the cefiderocol treated patients were allowed only one additional Gram-negative antibiotic used as adjunctive treatment, except for cUTI patients where only monotherapy was allowed. There was no fixed control drug or regimen because standard of care differed depending on the specific pathogen, the site of infection, and the local availability of different antibiotics in this global clinical study. The study was designed as an open-label trial because BAT was not a uniform treatment regimen and as such, it was impossible to blind the treatment. Possible biases that could happen in an open label trial include: 1) awareness of the intervention assigned to participants can introduce ascertainment bias in the measurement of outcomes, 2) performance bias in the decision to discontinue or modify study interventions, concomitant interventions, or other aspects of care; and 3) exclusion/attrition bias in the decision to withdraw from the trial or to exclude a participant from the analysis (Chan, 2013).

The study design was broadly inclusive, with entry criteria enabling investigators to enroll patients with different infection types and many comorbid conditions. The minimum criterion for eligibility was identification of a carbapenem-resistant Gram-negative pathogen through susceptibility testing, rapid diagnostic tests or failure of prior antibiotics. The study enrolled three infection types; 45% of patients had hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP) or healthcare-associated pneumonia (HCAP); 31% had blood stream infections (BSI) and/or sepsis; and 24% had cUTIs. BSIs or sepsis could have been secondary to any source of infection.

The initial evidence of carbapenem-resistant Gram-negative bacterial pathogen was derived from various scenarios as follows:

- Empiric treatment had failed and the target pathogen had been identified as a carbapenem-resistant (CR) Gram-negative pathogen
- Rapid diagnostic tests identifying the presence of carbapenemase or selective chromogenic media could be used to identify carbapenem-resistant Gram-negative bacterial infections prior to the availability of MIC results for the specific infection. Current hospital antibiogram for Gram-negative bacteria showing a CR rate of more than 90% was taken as evidence of CR for the isolated Gram-negative pathogens from the patient.
- Patient was known to be colonized (as evidenced by prior cultures from the same site as the infection) with a carbapenem-resistant Gram-negative pathogen prior to developing acute infection, ie, prior culture within the previous 72 hours
- An identified infection with *S. maltophilia* was eligible because it is inherently carbapenem resistant.

Most patients entered the study through traditional microbiological identification and susceptibility testing and therefore, most patients (>70%) were considered treatment failures of prior antibiotics at the time of randomization. For the primary efficacy analyses, only patients whose pathogen and carbapenem resistance susceptibility was confirmed by the central microbiology laboratory were included in the CR-mITT population.

Key exclusion criteria were:

1. Subjects who needed more than 3 systemic antibiotics as part of BAT for the treatment of the Gram-negative infection (subjects with mixed Gram-positive or anaerobic infections may have received appropriate concomitant narrow-spectrum antibiotics [eg, vancomycin, linezolid, metronidazole, clindamycin])
2. Subjects with co-infection caused by invasive aspergillosis, mucormycosis, or other highly lethal mold
3. Subjects who had central nervous system infection (eg, meningitis, brain abscess, shunt infection)
4. Subjects with infection requiring > 3 weeks of antibiotic treatment (eg, bone and joint infection, endocarditis)
5. Subjects with cystic fibrosis or moderate to severe bronchiectasis
6. Subjects in refractory septic shock defined as persistent hypotension despite adequate fluid resuscitation or despite vasopressor therapy at the time of Randomization
7. Subjects with severe neutropenia, ie, polymorphonuclear neutrophils < 100 cells/ $\mu$ L
8. Female subjects who had a positive pregnancy test at Screening or who were lactating

9. Subjects with Acute Physiology and Chronic Health Evaluation II (APACHE II) score > 30
10. Subjects who had received a potentially effective antibiotic regimen for the carbapenem-resistant Gram-negative infection for a continuous duration of more than 24 hours in cUTI, or 36 hours in HAP/VAP/HCAP or BSI/sepsis during the 72 hours prior to Randomization

These limited exclusion criteria allowed inclusion of patients with progressive disease and life-threatening or end-of-life conditions at the time of randomization. Due to the inclusive design of the CREDIBLE-CR study, many of the patients were critically and terminally ill at the time of randomization.

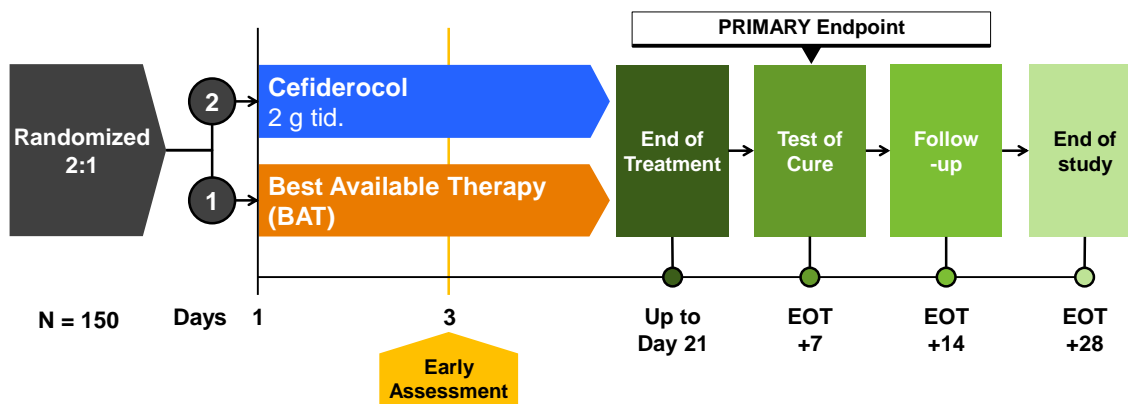
Patients were stratified at randomization by their infection site (HAP/VAP/HCAP, cUTI, and BSI/sepsis), baseline Acute Physiology and Chronic Health Evaluation II (APACHE II) score ( $\leq 15$  and  $\geq 16$ ) and region (N. America, S. America, Europe, and Asia-Pacific). This results in 24 different strata.

The CREDIBLE-CR study randomized 152 (treated 150) patients with evidence of CR Gram-negative infections at 100 sites in 17 countries covering 4 regions: Asia-Pacific, Europe, North America, and South America. Patients were randomized 2:1 to cefiderocol or BAT (Figure 20). The primary endpoint was clinical outcome at TOC for patients with HAP/VAP/HCAP and BSI/sepsis and microbiological outcome at TOC for patients with cUTIs.

The CREDIBLE-CR study was not designed or powered to conduct hypothesis testing in order to compare treatment groups; the objectives were to provide descriptive statistics, and there were no prespecified hypotheses. Patient-level information was extensively collected and analyzed in patient narratives and chronographs.

The sample size was based on the ability to recruit patients. The open-label design, the sample size determined on the basis of recruitment feasibility, the lack of prespecified hypotheses and the heterogeneous population are among the reasons that differences between treatment arms are not tested for significance. However, to assist in interpretation of the results, some confidence intervals are provided.

**Figure 20 CREDIBLE-CR Study Design**

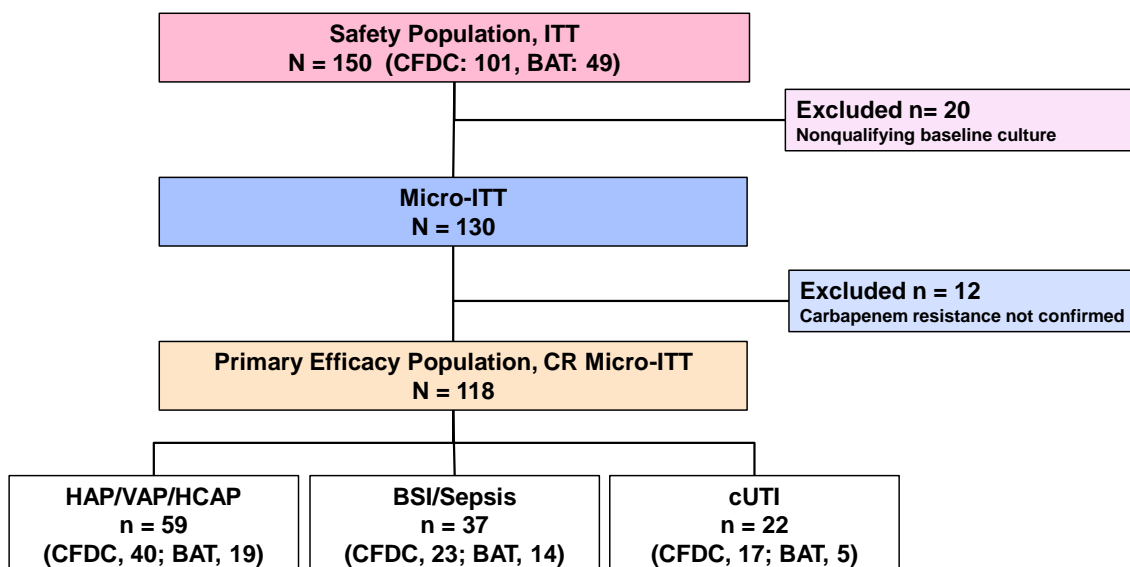


EOT, end of treatment; HAP, hospital-acquired pneumonia; tid, three times daily; TOC, test of cure; VAP, ventilator-associated pneumonia.

## 10.2 CREDIBLE-CR Analysis Population and Disposition

Figure 21 presents the disposition of all randomized patients.

**Figure 21 CREDIBLE-CR Disposition and Analysis Populations**



BAT, best available therapy; BSI, blood stream infection; CFDC, cefiderocol; CR, carbapenem resistant; CR Micro-ITT, Carbapenem-Resistant Microbiological Intent-to-Treat Population; cUTI, complicated urinary tract infection; HAP, hospital-acquired pneumonia; HCAP, healthcare-associated pneumonia; ITT, intent-to-treat; VAP, ventilator-associated pneumonia.

## 10.3 CREDIBLE-CR Baseline Characteristics and Demographics

### 10.3.1 Demographics

The demographics and baseline characteristics of the Safety Population are provided in Table 21. The baseline characteristics differed for patients over the age of 65 years old (63.4% in the cefiderocol group vs. 44.9% in the BAT group) and patients with moderate or severe renal impairment (42.6% in the cefiderocol group and 30.6% in the BAT group). All other baseline characteristics were generally similar between the two groups.

Of the patients with HAP/VAP/HCAP, 71.1% (32/45) in the cefiderocol group and 81.8% (18/22) in the BAT group were ventilated at randomization. Baseline characteristics and demographics are summarized below in Table 21 and full details are provided in [Appendix 15.3](#).

**Table 21 Summary Demographic and Baseline Characteristics (Safety Population)**

	Cefiderocol N=101	BAT N=49
Age		
Mean (Median, range)	63.1 (69.0, 19-92)	63.0 (62.0, 19-92)
Age ≥65 (%)	63.4	44.9
Male (n, %)	66 (65.3)	35 (71.4)
Total APACHE II Score		
Mean	15.3	15.4
Median	15	14
Range	2-29	2-28
≥ 16 (%)	45.5	44.9
Creatinine Clearance (mL/min)		
Mean	85.7	88.8
Median	59.2	69.4
Range	9.4 - 539.6	4.6 – 270.8
Creatinine Clearance grading group (%) <sup>a</sup>		
≥120 mL/Min (ARC)	19.8	24.5
> 80 mL/min to < 120 mL/min (normal)	17.8	20.4
> 50 mL/min to 80 mL/min (mild)	19.8	24.5
30 mL/min to 50 mL/min (moderate)	22.8	16.3
< 30 mL/min (severe)	19.8	14.3
Clinical diagnosis at baseline (%)		
HAP/VAP/HCAP	44.6	44.9
HAP	19.8	14.3
VAP	23.8	26.5
HCAP	1.0	4.1
BSI/Sepsis	29.7	34.7
cUTI	25.7	20.4

	Cefiderocol N=101	BAT N=49
Severity of disease (%)		
Mild	5.0	8.2
Moderate	40.6	44.9
Severe	54.5	46.9
Baseline fever (n, %)		
≥ 38.0 grade Celsius	13.9	14.3
< 38.0 grade Celsius	85.1	81.6
Prior therapy <sup>b</sup> = Yes (%)	92.1	100
SOFA score (median, range)	4, 0 - 17	4, 0 - 16
CPIS score (median, range) <sup>c</sup>	5, 2 - 9	5, 0 - 7
Number of Gram-negative pathogens from appropriate specimen at baseline (n, %) <sup>d</sup>		
0	14.9	10.2
1	67.3	73.5
2	12.9	16.3
3	4.0	0
4	1.0	0

APACHE II = Acute Physiology and Chronic Health Evaluation II; ARC = augmented renal clearance; BAT = best available therapy; BSI = bloodstream infection; cIAI = complicated intra-abdominal infections; cUTI = complicated urinary tract infection; HAP = hospital-acquired pneumonia; HCAP = healthcare-associated pneumonia; SSSI = skin and skin structure infection; VAP = ventilator-associated pneumonia  
Percentage was calculated using the number of patients in the column heading as the denominator.

[a] Creatinine clearance was calculated using the Cockcroft-Gault formula  $[(140 - \text{age in years}) \times (\text{actual weight in kg})] / (72 \times \text{serum creatinine in mg/dL})$ ; multiply by 0.85 if female] based on data from the central laboratory.

[b] Prior antimicrobial therapy taken 2 weeks prior to randomization.

[c] Appropriate specimen as defined in the protocol.

[d] Only collected from patients with HAP/VAP/HCAP.

### 10.3.2 Baseline Study Drug Regimen for Gram-negative Pathogens

In the CR mITT population, 82.5% (66/80) of cefiderocol-treated patients received monotherapy, while 28.9% (11/38) of the patients in the BAT group received monotherapy (Table 22). A colistin-based regimen was given to 65.8% (25/38) of the patients in the BAT group. Colistin monotherapy was received by six patients in the BAT group, five patients in the BAT group received other monotherapy (amikacin, ceftazidime-avibactam, doripenem, fosfomycin, and gentamicin). Colistin was a prohibited medication in the cefiderocol group; however, one patient received cefiderocol and colistin. A triple regimen was not allowed in the cefiderocol group; however, one patient received cefiderocol, gentamicin, and tigecycline.

**Table 22**                      **Summary of Study Drug Regimen for Gram-negative Pathogen at Day 1 and Day 2 (Carbapenem-resistant Microbiological Intent-to-treat Population)**

Study Drug Regimen	Cefiderocol (N = 80) n (%)	Study Drug Regimen	BAT (N = 38) n (%)
Cefiderocol Monotherapy	66 (82.5)	BAT Monotherapy	11 (28.9)
		Colistin	6 (15.8)
		Amikacin	1 (2.6)
		Ceftazidime-avibactam	1 (2.6)
		Doripenem	1 (2.6)
		Fosfomycin	1 (2.6)
		Gentamicin	1 (2.6)
Cefiderocol + Adjunctive Therapy	14 (17.5)	BAT Combination Therapy	27 (71.1)
Cefiderocol, Tigecycline	4 (5.0)	Colistin-based regimen	19 (50.0)
Cefiderocol, Fosfomycin	2 (2.5)	Colistin, Tigecycline	3 (7.9)
Cefiderocol, Amikacin	1 (1.3)	Colistin, Ampicillin-sulbactam	2 (5.3)
Cefiderocol, Ampicillin-sulbactam	1 (1.3)	Colistin, Fosfomycin	2 (5.3)
Cefiderocol, Ciprofloxacin	1 (1.3)	Colistin, Amikacin	1 (2.6)
Cefiderocol, Colistin	1 (1.3)	Colistin, Amikacin, Levofloxacin	1 (2.6)
Cefiderocol, Gentamicin	1 (1.3)	Colistin, Cefepime	1 (2.6)
Cefiderocol, Gentamicin, Tigecycline	1 (1.3)	Colistin, Cefepime, Tigecycline	1 (2.6)
Cefiderocol, Levofloxacin	1 (1.3)	Colistin, Cefoperazone-sulbactam	1 (2.6)
Cefiderocol, Piperacillin- tazobactam	1 (1.3)	Colistin, Ceftolozane-Tazobactam	1 (2.6)
		Colistin, Ertapenem	1 (2.6)
		Colistin, Imipenem-cilastatin	1 (2.6)
		Colistin, Meropenem	1 (2.6)
		Colistin, Piperacillin	1 (2.6)
		Colistin, Piperacillin-tazobactam	1 (2.6)
		Polymyxin B, Ampicillin- sulbactam, Fosfomycin	1 (2.6)
		Amikacin, Ceftazidime-avibactam	1 (2.6)
		Amikacin, Doripenem	1 (2.6)
		Ceftazidime, Ciprofloxacin	1 (2.6)
		Ceftazidime-avibactam, Gentamicin	1 (2.6)
		Ciprofloxacin, Trimethoprim- sulfamethoxazole	1 (2.6)
		Doripenem, Gentamicin	1 (2.6)
		Doripenem, Tobramycin	1 (2.6)
		Imipenem-cilastatin, Tigecycline	1 (2.6)
		Non-colistin-based regimen	8 (21.1)

BAT = best available therapy

Percentage was calculated using the number of patients in the column heading as the denominator. Study drug regimen includes antibiotics for Gram-negative pathogens that were taken after first study drug administration not including concomitant therapy.

### 10.3.3 Baseline Pathogens

In the CR mITT Population (primary efficacy population), for all infection sites combined, *Acinetobacter baumannii*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* were the most frequently occurring baseline pathogens in both treatment groups (Table 23). All five patients with patients with isolates of *Stenotrophomonas maltophilia* were from the cefiderocol treatment group.

**Table 23** Distribution of Gram-negative Pathogens Isolated at Baseline (Carbapenem-resistant Microbiological Intent-to-treat Population)

Diagnosis Pathogen [a]	Cefiderocol (N = 80) n (%)	BAT (N = 38) n (%)
All Infection Sites Combined	N' = 80	N' = 38
<i>Acinetobacter baumannii</i>	37 (46.3)	17 (44.7)
<i>Klebsiella pneumoniae</i>	32 (40.0)	12 (31.6)
<i>Pseudomonas aeruginosa</i>	17 (21.3)	11 (28.9)
<i>Escherichia coli</i>	5 (6.3)	2 (5.3)
<i>Stenotrophomonas maltophilia</i>	5 (6.3)	0
<i>Acinetobacter nosocomialis</i>	2 (2.5)	0
<i>Enterobacter cloacae</i>	2 (2.5)	0
<i>Chryseobacterium indologenes</i>	1 (1.3)	0
<i>Klebsiella oxytoca</i>	1 (1.3)	0
<i>Klebsiella variicola</i>	1 (1.3)	1 (2.6)
<i>Serratia marcescens</i>	1 (1.3)	0
<i>Enterobacter asburiae</i>	0	1 (2.6)
<i>Morganella morganii</i>	0	1 (2.6)
<i>Providencia stuartii</i>	0	1 (2.6)
HAP/VAP/HCAP	N' = 40	N' = 19
<i>Acinetobacter baumannii</i>	26 (65.0)	10 (52.6)
<i>Pseudomonas aeruginosa</i>	11 (27.5)	6 (31.6)
<i>Klebsiella pneumoniae</i>	10 (25.0)	5 (26.3)
<i>Stenotrophomonas maltophilia</i>	5 (12.5)	0
<i>Acinetobacter nosocomialis</i>	2 (5.0)	0
<i>Enterobacter cloacae</i>	2 (5.0)	0
<i>Escherichia coli</i>	2 (5.0)	2 (10.5)
<i>Chryseobacterium indologenes</i>	1 (2.5)	0
<i>Klebsiella oxytoca</i>	1 (2.5)	0
<i>Serratia marcescens</i>	1 (2.5)	0
<i>Enterobacter asburiae</i>	0	1 (5.3)
<i>Klebsiella variicola</i>	0	1 (5.3)

<b>Diagnosis Pathogen [a]</b>	<b>Cefiderocol (N = 80) n (%)</b>	<b>BAT (N = 38) n (%)</b>
BSI/Sepsis	N' = 23	N' = 14
<i>Klebsiella pneumoniae</i>	11 (47.8)	4 (28.6)
<i>Acinetobacter baumannii</i>	10 (43.5)	7 (50.0)
<i>Escherichia coli</i>	2 (8.7)	0
<i>Pseudomonas aeruginosa</i>	2 (8.7)	3 (21.4)
<i>Klebsiella variicola</i>	1 (4.3)	0
<i>Morganella morganii</i>	0	1 (7.1)
<i>Providencia stuartii</i>	0	1 (7.1)
cUTI	N' = 17	N' = 5
<i>Klebsiella pneumoniae</i>	11 (64.7)	3 (60.0)
<i>Pseudomonas aeruginosa</i>	4 (23.5)	2 (40.0)
<i>Acinetobacter baumannii</i>	1 (5.9)	0
<i>Escherichia coli</i>	1 (5.9)	0

BAT = best available therapy; BSI = bloodstream infection; cUTI = complicated urinary tract infection; HAP = hospital-acquired pneumonia; HCAP = healthcare-associated pneumonia; VAP = ventilator-associated pneumonia

Some patients experienced more than one pathogen.

Percentage was calculated using N' as the denominator, where N' is the number of patients who had the specified diagnosis.

Baseline pathogens were determined from appropriate clinical specimens collected within the 3 days prior to the first administration of study drug for patients who had been treated previously with an empiric antibiotic regimen and failed treatment, both clinically and microbiologically. For the other patients, baseline pathogens were determined from appropriate specimens collected within the 48 hours prior to the start of the first administration of study drug.

[a] Gram-negative pathogens were based on data from the central microbiology laboratory (if available).

## 10.4 Duration of Study Drug Treatment

In the CREDIBLE-CR study, the recommended duration of treatment with intravenous study drugs was 7 to 14 days in the hospital, (extended up to 21 days based on the investigator's clinical assessment of the patient) consistent with published treatment guidelines for serious infections. For patients with cUTI only, the investigator could have chosen to stop treatment after a minimum of 5 days if it was in the best interest of the patient.

In the CR mITT Population, in patients with HAP/VAP/HCAP or BSI/sepsis, 60.3% (38/63) in the cefiderocol group and 66.7% (22/33) in the BAT group had 7 to ≤ 14 days of exposure (Table 24). In patients with cUTI, 52.9% (9/17) in the cefiderocol group and 40.0% (2/5) in the BAT group had 7 to ≤ 14 days of exposure. Six patients in the cefiderocol group and no patients in the BAT group received study drug for less than 4 calendar days. One patient in the cefiderocol group received study drug treatment for 29 days due to orchiepididymitis

**Table 24 CREDIBLE-CR Duration of Exposure (CR Micro-ITT Population)**

<b>Parameter Statistic/Category</b>	<b>CFDC n = 80</b>	<b>BAT n = 38</b>
<b>HAP/VAP/HCAP or BSI/Sepsis</b>	<b>n = 63</b>	<b>n = 33</b>
Duration of exposure, days <sup>a</sup>		
Mean ± SD	11.4 ± 5.3	12.6 ± 4.4
Median (min, max)	11.0 (2, 22)	13.0 (2, 22)
Duration of exposure category, n (%)		
< 5 days	6 (9.5)	2 (6.1)
5 to < 7 days	3 (4.8)	0
7 to ≤ 14 days	38 (60.3)	22 (66.7)
> 14 days	16 (25.4)	9 (27.3)
<b>cUTI</b>	<b>n = 17</b>	<b>n = 5</b>
Duration of exposure, days <sup>a</sup>		
Mean ± SD	11.9 ± 7.1	7.4 ± 2.2
Median (min, max)	10.0 (2, 29)	6.0 (6, 11)
Duration of exposure category, n (%)		
< 5 days	2 (11.8)	0
5 to < 7 days	1 (5.9)	3 (60.0)
7 to ≤ 14 days	9 (52.9)	2 (40.0)
> 14 days	5 (29.4)	0

BAT, best available therapy; BSI, bloodstream infection; CFDC, cefiderocol; cUTI, complicated urinary tract infection; HAP, hospital acquired pneumonia; HCAP, healthcare-associated pneumonia; SD, standard deviation; VAP, ventilator-associated pneumonia.

a. Duration of exposure to study drug (days) = last dose date of study drug – 1<sup>st</sup> dose date of study drug + 1.

## 10.5 CREDIBLE-CR Efficacy

### 10.5.1 Study Efficacy Outcome – Clinical Definition

The clinical outcomes of clinical cure, clinical failure, or indeterminate (for EA, EOT, and TOC) and sustained clinical cure, relapse, indeterminate, or clinical failure (for FU) were assessed by the investigator according to the criteria established for each infection site as described in [Appendix 15.4](#). In case treatment duration was extended beyond 14 days, an additional clinical outcome was assessed on Day 14.

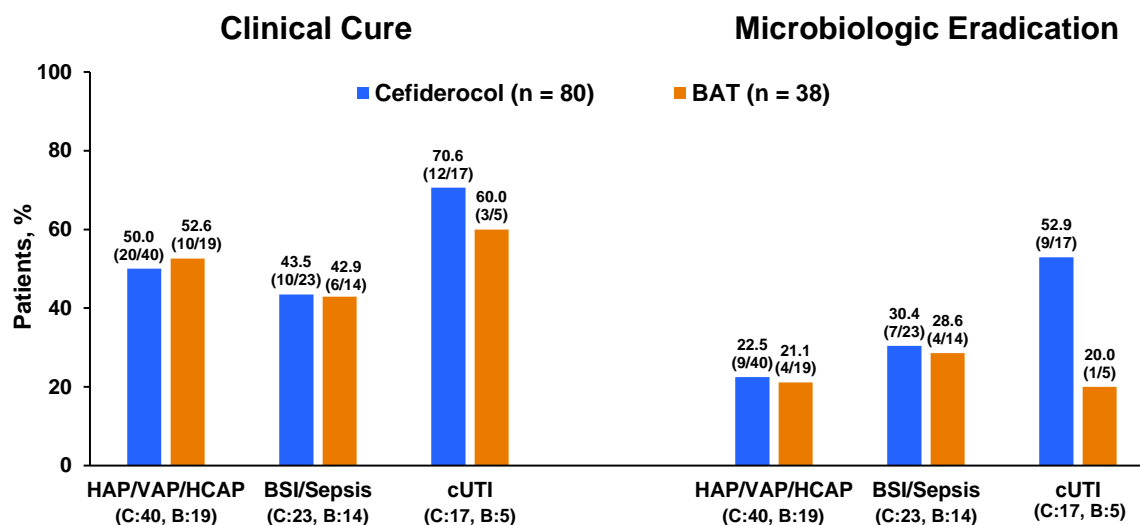
### 10.5.2 Study Efficacy Outcome – Microbiological Definition

Microbiological outcomes by baseline pathogen were determined by the sponsor according to the criteria established for each infection site at EA, EOT, TOC, and FU as presented in [Appendix 15.5](#). An overall per-patient microbiological outcome was also determined by the sponsor. In case treatment duration was extended beyond 14 days, an additional microbiological outcome was assessed on Day 14.

### 10.5.3 Outcomes by Time point

In the CR Micro-ITT population, clinical cure rates for all infection sites combined at EOT, TOC, and FU in patients treated with cefiderocol compared with those treated with BAT are presented in Table 25 and were 66.3% vs. 57.9%, 52.5% vs. 50.0%, and 47.5% vs. 34.2%, respectively, and clinical failure rates were 25.0% vs. 39.5%, 33.8% vs. 36.8%, and 33.8% vs. 36.8%, respectively. Likewise, microbiologic eradication rates for cefiderocol vs. BAT at EOT, TOC, and FU were 47.5% vs. 26.3%, 31.3% vs. 23.7%, and 26.3% vs. 18.4%, respectively, and microbiologic failure rates were 20.0% vs. 26.3% for all three time points. Similar results were observed for the mITT Population. The TOC time point was predefined as the primary time point. The clinical cure and microbiological eradication rates by infection site are shown in Figure 22, and a summary of clinical and microbiological outcomes for all infection sites combined and by infection site is shown in Table 25.

**Figure 22 CREDIBLE-CR Primary Endpoints at TOC by Infection Site (CR Micro-ITT Population)**



BAT, best available therapy; BSI, bloodstream infection; CR, carbapenem resistant; cUTI, complicated urinary tract infection; HAP, hospital acquired pneumonia; HCAP, healthcare-associated pneumonia; ITT, intent-to-treat; VAP, ventilator-associated pneumonia.

**Table 25 CREDIBLE-CR Summary by Time Point and Infection Site (CR Micro-ITT Population)**

	CFDC n = 80				BAT n = 38			
	All Infection Sites N=80	HAP/VAP/ HCAP n = 40	BSI/ Sepsis n = 23	cUTI n = 17	All Infection Sites N=38	HAP/VAP/ HCAP n = 19	BSI/ Sepsis n = 14	cUTI n = 5
<b>EOT, n/N (%)</b>								
Clinical cure	53/80 (66.3)	24/40 (60.0)	16/23 (69.6)	13/17 (76.5)	22/38 (57.9)	12/19 (63.2)	7/14 (50.0)	3/5 (60.0)
Clinical failure	20/80 (25.0)	13/40 (32.5)	6/23 (26.1)	1/17 (5.9)	15/38 (39.5)	7/19 (36.8)	7/14 (50.0)	1/5 (20.0)
Eradication	38/80 (47.5)	12/40 (30.0)	14/23 (60.9)	12/17 (70.6)	10/38 (26.3)	5/19 (26.3)	4/14 (28.6)	1/5 (20.0)
Persistence	16/80 (20.0)	15/40 (37.5)	1/23 (4.3)	0	10/38 (26.3)	9/19 (47.4)	1/14 (7.1)	0
<b>TOC, n/N (%)</b>								
Clinical cure	42/80 (52.5)	20/40 (50.0)	10 /23 (43.5)	12/17 (70.6)	19/38 (50.0)	10/19 (52.6)	6/14 (42.9)	3/5 (60.0)
Clinical failure	27/80 (33.8)	16/40 (40.0)	9/23 (39.1)	2/17 (11.8)	14/38 (36.8)	6/19 (31.6)	7/14 (50.0)	1/5 (20.0)
Eradication	25/80 (31.3)	9/40 (22.5)	7/23 (30.4)	9/17 (52.9)	9/38 (23.7)	4/19 (21.1)	4/14 (28.6)	1/5 (20.0)
Persistence	16/80 (20.0)	8/40 (20.0)	3/23 (13.0)	5/17 (29.4)	10/38 (26.3)	7/19 (36.8)	2/14 (14.3)	1/5 (20.0)
<b>FU, n/N (%)</b>								
Clinical cure	38/80 (47.5)	20/40 (50.0)	9/23 (39.1)	9/17 (59.2)	13/38 (34.2)	6/19 (31.6)	4/14 (28.6)	3/5 (60.0)
Clinical failure	27/80 (33.8)	16/40 (40.0)	9/23 (39.1)	2/17 (11.8)	14/38 (36.8)	6/19 (31.6)	7/14 (50.0)	1/5 (20.0)
Eradication	21/80 (26.3)	8/40 (20.0)	6/23 (26.1)	7/17 (41.2)	7/38 (18.4)	3/19 (15.8)	3/14 (21.4)	1/5 (20.0)
Persistence	16/80 (20.0)	8/40 (20.0)	3/23 (13.0)	5/17 (29.4)	10/38 (26.3)	7/19 (36.8)	2/14 (14.3)	1/5 (20.0)

BAT, best available therapy; BSI, bloodstream infection; CFDC, cefiderocol; CR, carbapenem resistant; cUTI, complicated urinary tract infection; EOT, end of treatment; FU, follow-up; HAP, hospital acquired pneumonia; HCAP, healthcare-associated pneumonia; ITT, intent-to-treat; TOC, test of cure; VAP, ventilator-associated pneumonia.

#### 10.5.4 Outcomes by Baseline Pathogen

The three pathogens isolated with the highest frequency in this study were CR *A. baumannii*, CR *K. pneumoniae*, and CR *P. aeruginosa*. Outcomes for these pathogens are presented in Table 26.

**Table 26 CREDIBLE-CR Outcomes at Test of Cure by Baseline CR Pathogen (CR Micro-ITT Population)**

TOC	Cefiderocol n = 80 n/N (%)	BAT n = 38 n/N (%)
<b>Clinical cure</b>		
CR <i>A. baumannii</i>	16/37 (43.2)	9/17 (52.9)
CR <i>P. aeruginosa</i>	7/12 (58.3)	5/10 (50.0)
CR <i>K. pneumoniae</i>	18/27 (66.7)	6/12 (50.0)
<b>Clinical failure</b>		
CR <i>A. baumannii</i>	17/37 (45.9)	6/17 (35.3)
CR <i>P. aeruginosa</i>	3/12 (25.0)	4/10 (40.0)
CR <i>K. pneumoniae</i>	5/27 (18.5)	4/12 (33.3)
<b>Eradication</b>		
CR <i>A. baumannii</i>	10/37 (27.0)	5/17 (29.4)
CR <i>P. aeruginosa</i>	1/12 (8.3)	2/10 (20.0)
CR <i>K. pneumoniae</i>	13/27 (48.1)	3/12 (25.0)
<b>Persistence</b>		
CR <i>A. baumannii</i>	5/37 (13.5)	4/17 (23.5)
CR <i>P. aeruginosa</i>	4/12 (33.3)	2/10 (20.0)
CR <i>K. pneumoniae</i>	4/27 (14.8)	4/12 (33.3)

BAT, best available therapy; CR, carbapenem-resistant; ITT, intent-to-treat; TOC, test of cure.

#### 10.5.5 Outcomes by Treatment Regimen

Study drug regimens were categorized into monotherapy and combination therapy, and the BAT study drug regimens were further classified into colistin-based or non-colistin based regimens, to understand if there was any difference in the clinical cure rate or microbiological eradication rate at TOC between these subgroups. The results are shown in [Table 27](#) and [Table 28](#).

**Table 27**                      **Number and Proportion of Patients with Clinical Cure at Test of Cure by Study Drug Regimen for Gram-negative Pathogen at Day 1 and Day 2 (CR-mITT Population)**

Study Drug Regimen	Cefiderocol (N = 80) n/N' (%)	Study Drug Regimen	BAT (N = 38) n/N' (%)
Cefiderocol Monotherapy	35/66 (53.0)	BAT Monotherapy	7/11 (63.6)
		- Colistin	4/6 (66.7)
		- Non-colistin	3/5 (60.0)
Cefiderocol Combination Therapy	7/14 (50.0)	BAT Combination Therapy	12/27 (44.4)
		- Colistin-based	8/19 (42.1)
		- Non-colistin based	4/8 (50.0)

BAT = best available therapy

**Table 28**                      **Number and Proportion of Patients with Microbiological Eradication at Test of Cure by Study Drug Regimen for Gram-negative Pathogen at Day 1 and Day 2 (CR-mITT Population)**

Study Drug Regimen	Cefiderocol (N = 80) n/N' (%)	Study Drug Regimen	BAT (N = 38) n/N' (%)
Cefiderocol Monotherapy	21/66 (31.8)	BAT Monotherapy	4/11 (36.4)
		- Colistin-based	3/6 (50.0)
		- Non-colistin based	1/5 (20.0)
Cefiderocol Combination Therapy	4/14 (28.6)	BAT Combination Therapy	5/27 (18.5)
		- Colistin-based	4/19 (21.1)
		- Non-colistin based	1/8 (12.5)

BAT = best available therapy

## 10.6 CREDIBLE-CR Safety

### 10.6.1 Overview of Adverse Events

Over 90% of the patients in each treatment group had at least one adverse event ([Table 29](#)). The incidence of adverse events considered by the investigator to be treatment-related was 14.9% in the cefiderocol group and 22.4% in the BAT group. The percentage of reported serious adverse events was 49.5% in the cefiderocol group and 46.9% in the BAT group. Overall, six patients experienced treatment-related serious adverse events (one in the cefiderocol group and five in the BAT group). The percentage of discontinuations due to adverse events was 9.9% in the cefiderocol group and 6.1% in the BAT group. Adverse events leading to death were reported in 33.7% and 18.4% in the cefiderocol group and the BAT group, respectively.

**Table 29 Overview of Treatment-emergent Adverse Events (Safety Population)**

Adverse Event Category	Cefiderocol (N = 101)		BAT (N = 49)	
	Patients n (%)	Events n'	Patients n (%)	Events n'
AEs	92 (91.1)	634	47 (95.9)	311
Treatment-related AEs	15 (14.9)	27	11 (22.4)	16
SAEs	50 (49.5)	92	23 (46.9)	36
Treatment-related SAEs	1 (1.0)	1	5 (10.2)	7
Discontinuation due to AEs	10 (9.9)	12	3 (6.1)	3
Discontinuation due to treatment-related AEs	3 (3.0)	3	2 (4.1)	2
Adverse Events Leading to Death	34 (33.7)	45	9 (18.4)	14

AEs = adverse events; BAT = best available therapy; SAEs = serious adverse events

Percentage is calculated using the number of patients in the column heading as the denominator. Adverse events that started after the first dose of the study drug and up to End of Study visit are defined as treatment-emergent.

One patient received cefiderocol after completion of BAT; this patient is included under BAT in this table.

### 10.6.2 Adverse Events by Preferred Term Classification

Adverse events reported for  $\geq 5\%$  subjects in either treatment group are presented in [Table 30](#). The most frequently ( $\geq 10\%$ ) reported AEs in the cefiderocol arm were diarrhea, pyrexia, septic shock and vomiting. Adverse events reported more frequently ( $> 5\%$  difference between the treatment groups) in the cefiderocol group than in the BAT group were diarrhea, ALT increased, AST increased, pleural effusion, and chest pain. Adverse events reported less frequently ( $> 5\%$  difference between the treatment groups) in the cefiderocol group than in the BAT group were hypokalemia, hyperkalemia, rash, and depression.

Each patient with an adverse event of alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, and/or chest pain (events that were more frequent in the cefiderocol group than in the BAT group) were specifically reviewed in detail to determine if these were adverse drug reactions. Patients with AST increased were reviewed together with patients with ALT increased. For ALT/AST increased, an underlying disease or concomitant medication existing as confounding factors or an alternative etiology was suggested for most of the patients, although two patients had increases considered to be related to cefiderocol by the investigators. Transient elevations in liver enzymes due to cefiderocol cannot be excluded; however, like other cephalosporins, the elevations were reversible after discontinuing the study drug, and none resulted in serious hepatotoxicity.

All six chest pain cases were in the cefiderocol group. Five of the six cases were considered to be non-cardiovascular in nature and not related to cefiderocol. One patient had a medical history of acute myocardial infarction three months before randomization,

and the adverse event of chest pain was treated with nitroglycerin, oral isosorbide dinitrate, diltiazem, nicorandil, and trimetazidine. The remaining patients experienced chest pain that recovered with no treatment and while continuing to receive the study drug or recovered after administration of nonsteroidal anti-inflammatory drugs or opioids, suggesting a non-cardiovascular nature of pain.

The majority of the remaining adverse events occurred at a low frequency and were considered manifestations of the patients' underlying disease.

**Table 30 Adverse Events Occurring in  $\geq 5\%$  of Subjects in Either Treatment Group (Safety Population)**

<b>Preferred Term</b>	<b>Cefiderocol (N = 101) n (%)</b>	<b>BAT (N = 49) n (%)</b>
Subjects with adverse events	92 (91.1)	47 (95.9)
<b>Diarrhoea</b>	<b>19 (18.8)</b>	<b>6 (12.2)</b>
Pyrexia	14 (13.9)	6 (12.2)
Septic shock	13 (12.9)	7 (14.3)
Vomiting	13 (12.9)	7 (14.3)
Decubitus ulcer	10 (9.9)	4 (8.2)
<i>Hypokalaemia</i>	9 (8.9)	7 (14.3)
Liver function test abnormal	8 (7.9)	4 (8.2)
Constipation	8 (7.9)	3 (6.1)
Hypotension	8 (7.9)	3 (6.1)
Anaemia	8 (7.9)	2 (4.1)
<b>Aspartate aminotransferase increased</b>	<b>8 (7.9)</b>	<b>1 (2.0)</b>
<b>Pleural effusion</b>	<b>8 (7.9)</b>	<b>1 (2.0)</b>
Acute kidney injury	7 (6.9)	5 (10.2)
Dyspnoea	7 (6.9)	2 (4.1)
Nausea	7 (6.9)	2 (4.1)
Pneumonia	7 (6.9)	1 (2.0)
<b>Alanine aminotransferase increased</b>	<b>7 (6.9)</b>	<b>0</b>
Abdominal pain	6 (5.9)	4 (8.2)
Hypomagnesaemia	6 (5.9)	4 (8.2)
Thrombocytopenia	6 (5.9)	4 (8.2)
<b>Chest pain</b>	<b>6 (5.9)</b>	<b>0</b>
<i>Hyperkalaemia</i>	5 (5.0)	6 (12.2)
Agitation	5 (5.0)	2 (4.1)
Oedema peripheral	5 (5.0)	2 (4.1)
Sepsis	4 (4.0)	3 (6.1)
<i>Rash</i>	3 (3.0)	4 (8.2)
Bradycardia	3 (3.0)	3 (6.1)
Metabolic acidosis	3 (3.0)	3 (6.1)
Insomnia	2 (2.0)	3 (6.1)
<i>Depression</i>	0	3 (6.1)

BAT = best available therapy

Percentage was calculated using the number of subjects in the column heading as the denominator. Adverse events that started after the first dose of the study drug and up to End of Study visit were defined as treatment-emergent. One subject received cefiderocol after completion of BAT; this subject is included under BAT in this table. The most frequently (> 10% of subjects in the cefiderocol arm) reported adverse events are shaded. Adverse events reported more frequently (> 5% difference between the treatment groups) in the cefiderocol group than in the BAT group are shown in bold. Adverse events reported less frequently (> 5% difference between the treatment groups) in the cefiderocol group than in the BAT group are shown in italics.

### 10.6.3 Treatment-related Treatment-emergent Adverse Events

Treatment-emergent adverse events considered to be treatment-related by the investigator were reported for 14.9% in the cefiderocol group and 22.4% in the BAT group. Diarrhea (2.0%), liver function test abnormal (2.0%), ALT increased (3.0%), and AST increased (3.0%) were the most frequently reported treatment-related treatment-emergent adverse events in the cefiderocol group (Table 31); while acute kidney injury (8.2%) was the most frequently reported treatment-related treatment-emergent adverse event in the BAT group.

**Table 31 Patients with Treatment-related Adverse Events by Preferred Term (Safety Population)**

Preferred Term	Cefiderocol (N = 101)	BAT (N = 49)
	n (%)	n (%)
Patients with treatment-related AEs	15 (14.9)	11 (22.4)
<b>Alanine aminotransferase increased</b>	<b>3 (3.0)</b>	<b>0</b>
<b>Aspartate aminotransferase increased</b>	<b>3 (3.0)</b>	<b>0</b>
<b>Diarrhoea</b>	<b>2 (2.0)</b>	<b>0</b>
<b>Liver function test abnormal</b>	<b>2 (2.0)</b>	<b>0</b>
Ascites	1 (1.0)	0
Blood creatinine increased	1 (1.0)	0
Blood pressure increased	1 (1.0)	0
Clostridium difficile colitis	1 (1.0)	0
Drug eruption	1 (1.0)	0
Dysgeusia	1 (1.0)	0
Hypertension	1 (1.0)	0
Hypokalaemia	1 (1.0)	0
Oedema	1 (1.0)	0
Pleural effusion	1 (1.0)	0
Pseudomembranous colitis	1 (1.0)	1 (2.0)
Pyrexia	1 (1.0)	0
Rash	1 (1.0)	0
Transaminases increased	1 (1.0)	0
Upper gastrointestinal haemorrhage	1 (1.0)	0
<b>Acute kidney injury</b>	<b>0</b>	<b>4 (8.2)</b>
Anaphylactic reaction	0	1 (2.0)
Blood creatine increased	0	1 (2.0)
Hepatic enzyme increased	0	1 (2.0)
Metabolic acidosis	0	1 (2.0)
Renal disorder	0	1 (2.0)

<b>Preferred Term</b>	<b>Cefiderocol (N = 101) n (%)</b>	<b>BAT (N = 49) n (%)</b>
Respiratory arrest	0	1 (2.0)
Sepsis	0	1 (2.0)
Septic shock	0	1 (2.0)
Status epilepticus	0	1 (2.0)
Vomiting	0	1 (2.0)

AEs = adverse events; BAT = best available therapy

Percentage was calculated using the number of patients in the column heading as the denominator. Adverse events that started after the first dose of the study drug and up to End of Study visit were defined as treatment-emergent. Although a patient may have had 2 or more adverse events, the patient was counted only once within a System Organ Class category. The same patient may have contributed to 2 or more Preferred Terms in the same System Organ Class category.

One patient received cefiderocol after completion of BAT; this patient is included under BAT in this table. The most frequently reported treatment-related treatment-emergent adverse events are shown in bold.

### 10.6.4 Serious Adverse Events

Serious adverse events were reported for 49.5% of patients in the cefiderocol group and 46.9% of patients in the BAT group. Septic shock was the most frequently reported serious adverse event in both the cefiderocol (11.9%; 12/101 patients) and BAT (12.2%; 6/49 patients) groups (Table 32).

**Table 32 Patients with Serious Adverse Events by System Organ Class and Preferred Term (Safety Population)**

<b>System Organ Class Preferred Term</b>	<b>Cefiderocol (N = 101) n (%)</b>	<b>BAT (N = 49) n (%)</b>
Patients with SAEs	50 (49.5)	23 (46.9)
Blood and lymphatic system disorders	1 (1.0)	1 (2.0)
Anaemia	0	1 (2.0)
Febrile neutropenia	1 (1.0)	0
Cardiac disorders	6 (5.9)	4 (8.2)
Bradycardia	1 (1.0)	1 (2.0)
Cardiac arrest	4 (4.0)	2 (4.1)
Cardiac failure congestive	1 (1.0)	0
Myocardial infarction	1 (1.0)	0
Pulseless electrical activity	0	1 (2.0)
Gastrointestinal disorders	5 (5.0)	0
Abdominal pain	1 (1.0)	0
Abdominal pain upper	1 (1.0)	0
Gastrointestinal haemorrhage	1 (1.0)	0
Intestinal ischaemia	1 (1.0)	0
Lower gastrointestinal haemorrhage	1 (1.0)	0
Pancreatitis	1 (1.0)	0

<b>System Organ Class Preferred Term</b>	<b>Cefiderocol (N = 101) n (%)</b>	<b>BAT (N = 49) n (%)</b>
Small intestinal obstruction	1 (1.0)	0
General disorders and administration site conditions	7 (6.9)	3 (6.1)
Chills	1 (1.0)	0
General physical health deterioration	0	1 (2.0)
Multi-organ failure	2 (2.0)	2 (4.1)
Pyrexia	3 (3.0)	0
Sudden death	1 (1.0)	0
Hepatobiliary disorders	3 (3.0)	0
Chronic hepatic failure	1 (1.0)	0
Hepatic failure	1 (1.0)	0
Hepatitis	1 (1.0)	0
Immune system disorders	0	1 (2.0)
Anaphylactic reaction	0	1 (2.0)
Infections and infestations	29 (28.7)	11 (22.4)
Bacteraemia	3 (3.0)	0
Bacterial infection	1 (1.0)	0
Device related infection	0	1 (2.0)
Empyema	1 (1.0)	1 (2.0)
Endocarditis	0	1 (2.0)
Enterococcal bacteraemia	1 (1.0)	0
Enterococcal infection	2 (2.0)	0
Meningitis	0	1 (2.0)
Necrotising fasciitis	0	1 (2.0)
Osteomyelitis	1 (1.0)	0
Osteomyelitis acute	0	1 (2.0)
Pneumonia	5 (5.0)	1 (2.0)
Pneumonia bacterial	1 (1.0)	0
Renal abscess	1 (1.0)	0
Sepsis	3 (3.0)	0
<b>Septic shock</b>	<b>12 (11.9)</b>	<b>6 (12.2)</b>
Systemic candida	1 (1.0)	0
Urinary tract infection	1 (1.0)	0
Urosepsis	1 (1.0)	0
Investigations	5 (5.0)	3 (6.1)
Liver function test abnormal	4 (4.0)	3 (6.1)
Transaminases increased	1 (1.0)	0
Metabolism and nutrition disorders	3 (3.0)	1 (2.0)
Hyponatraemia	1 (1.0)	0
Metabolic acidosis	2 (2.0)	1 (2.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1.0)	0

<b>System Organ Class Preferred Term</b>	<b>Cefiderocol (N = 101) n (%)</b>	<b>BAT (N = 49) n (%)</b>
Lung neoplasm malignant	1 (1.0)	0
Nervous system disorders	3 (3.0)	2 (4.1)
Dizziness	1 (1.0)	0
Hypoaesthesia	1 (1.0)	0
Neurological decompensation	1 (1.0)	0
Paraesthesia	1 (1.0)	0
Quadriplegia	0	1 (2.0)
Status epilepticus	0	1 (2.0)
Renal and urinary disorders	6 (5.9)	2 (4.1)
Acute kidney injury	3 (3.0)	2 (4.1)
Anuria	1 (1.0)	0
Nephrolithiasis	1 (1.0)	0
Oliguria	2 (2.0)	0
Respiratory, thoracic and mediastinal disorders	7 (6.9)	2 (4.1)
Acute respiratory failure	1 (1.0)	1 (2.0)
Chronic obstructive pulmonary disease	1 (1.0)	0
Obstructive airways disorder	1 (1.0)	0
Pneumonia aspiration	2 (2.0)	0
Respiratory arrest	0	1 (2.0)
Respiratory failure	2 (2.0)	0
Vascular disorders	2 (2.0)	2 (4.1)
Hypotension	2 (2.0)	1 (2.0)
Shock	1 (1.0)	1 (2.0)

BAT = best available therapy; SAEs = serious adverse events

Percentage was calculated using the number of patients in the column heading as the denominator. Adverse events that started after the first dose of the study drug and up to End of Study visit were defined as treatment-emergent. Although a patient may have had 2 or more adverse events, the patient was counted only once within a System Organ Class category. The same patient may have contributed to 2 or more Preferred Terms in the same System Organ Class category.

One patient received cefiderocol after completion of BAT; this patient is included under BAT in this table. The most frequently reported serious adverse event is shown in bold.

### 10.6.5 Treatment-related Serious Adverse Events

Treatment-related serious adverse events were reported in one patient (1.0%) in the cefiderocol group and five patients in the BAT group (10.2%). (Table 33).

The one cefiderocol treated patient had a treatment-related serious adverse event of transaminases increased, on day 5, which was considered severe, led to study drug discontinuation, and resolved in 30 days. The patient was enrolled with cUTI and had medical history of acute myocardial infarction, congestive heart failure, and ongoing bacteremia at the time of randomization. Alkaline phosphatase, gamma-

glutamyltransferase, and aspartate aminotransferase were increased at baseline; however, the patient had a normal hepatic ultrasound at the time of transaminase increase.

Summary details of the five patients in the BAT group for whom treatment-related serious adverse events are reported is given below:

One patient had a treatment-related serious adverse event of status epilepticus on Day 13; this patient received ciprofloxacin and ceftazidime as BAT, and the status epilepticus was considered related to ciprofloxacin.

One BAT-treated patient had treatment-related serious adverse events of metabolic acidosis, acute kidney injury, and respiratory arrest on Day 6, which led to the patient's death. These SAEs were considered to be due to colistin use.

One patient had a treatment-related serious adverse event of anaphylaxis after the first dose of BAT (ceftazidime/avibactam). This event was considered severe and led to study drug discontinuation. This event resolved.

One patient who received tigecycline and colistin as BAT had a treatment-related serious adverse event of acute kidney injury on Day 7, which was considered related to colistin use. The study drug dose was reduced and continued. This event was not resolved.

One patient who received tigecycline and colistin as BAT had a treatment-related serious adverse event of septic shock on Day 23, followed by 2 serious adverse events of cardiac arrest on Day 24 (considered not related to study drug), the second of which led to the patient's death. This patient had experienced clinical and microbiological failure.

**Table 33 Patients with Treatment-related Serious Adverse Events by System Organ Class and Preferred Term (Safety Population)**

<b>System Organ Class Preferred Term</b>	<b>Cefiderocol (N = 101) n (%)</b>	<b>BAT (N = 49) n (%)</b>
Patients with treatment-related SAEs	1 (1.0)	5 (10.2)
Immune system disorders	0	1 (2.0)
Anaphylactic reaction	0	1 (2.0)
Infections and infestations	0	1 (2.0)
Septic shock	0	1 (2.0)
Investigations	1 (1.0)	0
Transaminases increased	1 (1.0)	0
Metabolism and nutrition disorders	0	1 (2.0)
Metabolic acidosis	0	1 (2.0)
Nervous system disorders	0	1 (2.0)
Status epilepticus	0	1 (2.0)
Renal and urinary disorders	0	2 (4.1)
Acute kidney injury	0	2 (4.1)
Respiratory, thoracic and mediastinal disorders	0	1 (2.0)
Respiratory arrest	0	1 (2.0)

BAT = best available therapy; SAEs = serious adverse events

Percentage was calculated using the number of patients in the column heading as the denominator. Adverse events that started after the first dose of the study drug and up to End of Study visit were defined as treatment-emergent. Although a patient may have had 2 or more adverse events, the patient was counted only once within a System Organ Class category. The same patient may have contributed to 2 or more Preferred Terms in the same System Organ Class category.

One patient received cefiderocol after completion of BAT; this patient is included under BAT in this table.

#### 10.6.6 Liver-related Adverse Events

Liver-related AEs were more frequently reported in the cefiderocol group than in the BAT group. All cases were, however, recovered with or without discontinuation of Cefiderocol, and no case resulted in death.

Liver-related AEs, including liver biochemistry, occurred more frequently in the cefiderocol group than in the BAT group. Liver-related AEs, including those related to liver biochemistry and clotting tests, that occurred in 2 or more patients in either treatment group were the following: ALT increased (7/101, 6.9% and 0 patients in the cefiderocol and BAT groups, respectively), AST increased (8/101, 7.9% and 1/49, 2.0% of patients in the cefiderocol and BAT groups, respectively), and liver function test abnormal (8/101, 7.9% and 4/49, 8.2% of patients in the cefiderocol and BAT groups, respectively). In the cefiderocol group, most events were considered by the investigator to be mild or moderate in severity and not related to study drug, with the exception of patients which are detailed in [Appendix 15.6](#). Appendix 15.6 also provides listings on patients with abnormal liver chemistry values and treatment emergent hepatic disorders.

The percentage of patients meeting the predefined categories for abnormal liver biochemistry are as follows: ALT values  $> 3 \times \text{ULN}$  during the study occurred in 16.3% (16/98) of patients in the cefiderocol group and 8.3% (4/48) of patients in the BAT group. The percentage of patients who had ALT and/or AST  $> 3 \times \text{ULN}$  and TBL  $> 2 \times \text{ULN}$  or PT-INR  $> 1.5$  was 13.2% (12/91) in the cefiderocol group and 8.7% (4/46) in the BAT group.

The review of all relevant data demonstrated that there was no drug induced liver injury nor clinical and biochemical criteria meeting Hy's law in cefiderocol treated patients. Confounders were present in most cases. The possibility of the study drug having caused liver enzyme elevation cannot be completely ruled out; however, the changes were reversible, and none resulted in serious outcomes.

### 10.6.7 Renal Toxicity According to RIFLE Criteria

The degree of renal toxicity according to the RIFLE criteria (risk, injury, failure) from baseline to TOC is shown in Table 34.

**Table 34 Summary of Post Baseline Renal Abnormality by TOC (Safety Population)**

	<b>Cefiderocol (N = 101) n (%)</b>	<b>BAT (N = 49) n (%)</b>
Serum Cr 1.5 x to 2 x from baseline by TOC	15 (14.9)	7 (14.3)
<b>Serum Cr 2 x to 3 x from baseline by TOC</b>	<b>5 (5.0)</b>	<b>8 (16.3)</b>
Serum Cr $> 3x$ from baseline or (baseline $\geq 4$ mg/dL and serum Cr increase $\geq 0.5$ mg/dL)	1 (1.0)	2 (4.1)

Consistent with colistin use in the BAT arm, serum creatinine changes of 2 or more from baseline during exposure to treatment are more marked in the BAT arm.

### 10.7 CREDIBLE-CR Mortality

Although all-cause mortality at Day 14 and Day 28 in patients with HAP/VAP/HCAP and BSI/Sepsis was a secondary objective of the study, Shionogi analyzed all-cause mortality for all patients (Safety Population). There was a higher all-cause mortality rate in cefiderocol-treated patients compared with BAT-treated patients at all time points (Table 35).

**Table 35 CREDIBLE-CR All-cause Mortality (Safety Population)**

	Cefiderocol		BAT	
	n/N (%)	95 % CI	n/N (%)	95 % CI
<b>14-day mortality</b>	19/101 (18.8)	11.7, 27.8	6/49 (12.2)	4.6, 24.8
<b>28-day mortality</b>	25/101 (24.8)	16.7, 34.3	9/49 (18.4)	8.8, 32.0
<b>End of study<sup>a</sup></b>	34/101 (33.7)	24.6, 43.8	9/49 (18.4)	8.8, 32.0

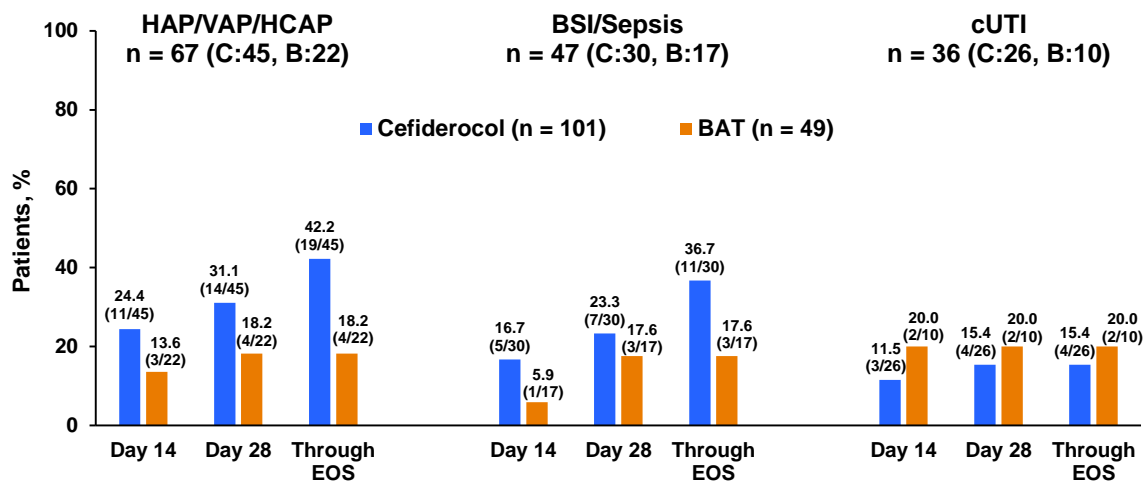
CI, confidence interval; EOS, end of study; FU, follow-up.

a. End of study: A variable time point that includes deaths through EOS visit (28 days after end of treatment, or date of withdrawal) and after EOS visit if death was due to an SAE that occurred prior to EOS visit.

After the study ended, 2 additional deaths in patients treated with cefiderocol and 5 additional deaths in patients treated with BAT were spontaneously reported through 108 days. These deaths total as follows: cefiderocol: 36/101 (35.6 %) vs. BAT: 14/49 (28.6 %).

At Day 14, Day 28, and end of study, all-cause mortality in the Safety Population was higher in patients with baseline HAP/VAP/HCAP and BSI/sepsis and lower in patients with baseline cUTI in the cefiderocol group compared with those in the BAT group (Figure 23).

**Figure 23 CREDIBLE-CR All-Cause Mortality by Infection Site (Safety Population)**



BAT, best available therapy; BSI, bloodstream infection; CR, carbapenem-resistant; EOS, end of study; HAP, hospital acquired pneumonia; HCAP, healthcare-associated pneumonia; ITT, intent-to-treat; VAP, ventilator-associated pneumonia.

The CREDIBLE-CR Study had no missing mortality data through EOS. However, there were spontaneous post-study reports of death provided to Shionogi, and they have been included for transparency in Table 35. Recognizing that the EOS (see footnote in Table 35 for definition) is variable for each patient, another way to view the data is strictly by relative day. Day 49 has been chosen as an additional timepoint and while Day 49 is a post-hoc defined time point, and not part of the study design or SAP, this time point does capture all 43 deaths collected through the end of study. In addition, it captures one

additional post-study-reported death from the BAT group. Therefore, the Day 49 row includes a total of 44 deaths. As per the protocol, there was no requirement to follow patients through Day 49, and the Sponsor collected information on all patients' survival status as per the protocol defined visits. Introducing a new time point after the study was completed creates the issue of how to account for patients who correctly completed the study and did not die during the study. There were 75 such patients, and in Table 36, they are imputed as surviving until Day 49. In addition, to show the entire time course for these patients a Kaplan-Meier Curve is given in Figure 24. In Figure 24, the "+" sign indicates a patient who was "censored" under the idea that Day 49 would be considered the end of the study.

**Table 36 Summary for All-cause Mortality through Day 49 (Safety Population)**

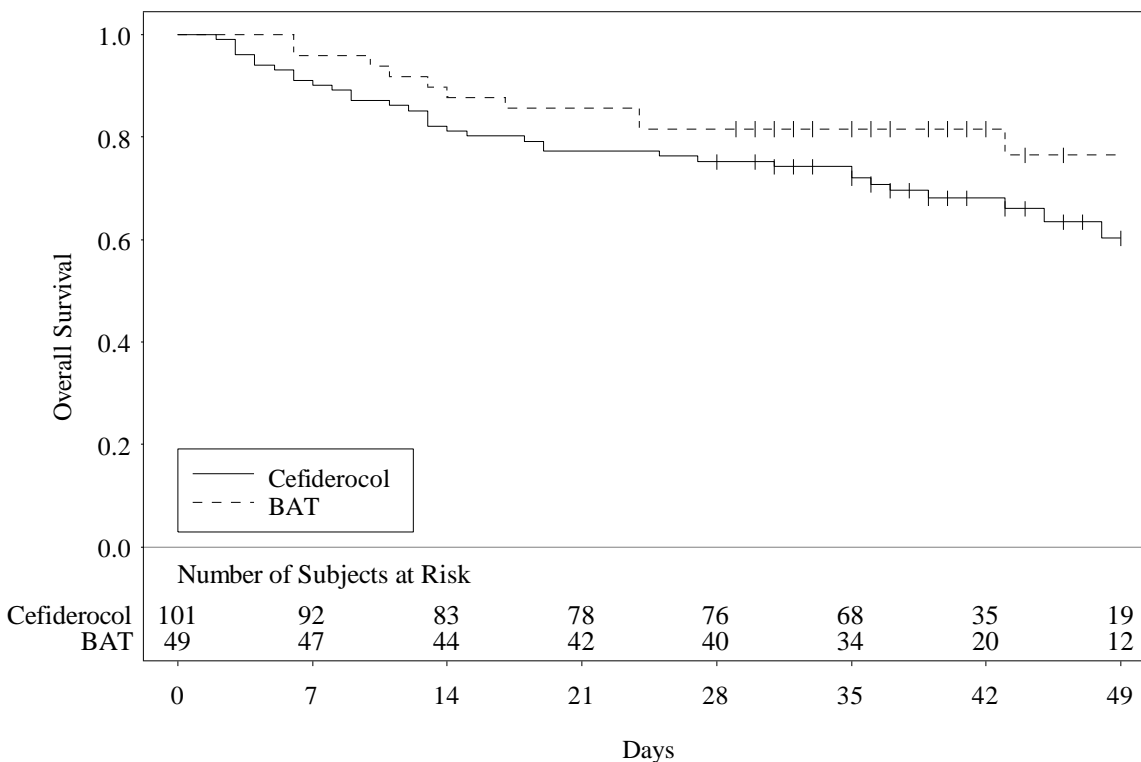
<b>Infection Site</b>	<b>Cefiderocol</b>		<b>BAT</b>	
<b>All-cause Mortality Rate</b>	<b>(N = 101)</b>		<b>(N = 49)</b>	
	<b>n/N (%)</b>	<b>95% CI</b>	<b>n/N (%)</b>	<b>95% CI</b>
<b>HAP/VAP/HCAP</b>	<b>N' = 45</b>		<b>N' = 22</b>	
Day 14	11/45 (24.4)	(12.9, 39.5)	3/22 (13.6)	(2.9, 34.9)
Day 28	14/45 (31.1)	(18.2, 46.6)	4/22 (18.2)	(5.2, 40.3)
Day 49	19/45 (42.2)	(27.7, 57.8)	4/22 (18.2)	(5.2, 40.3)
<b>BSI/Sepsis</b>	<b>N' = 30</b>		<b>N' = 17</b>	
Day 14	5/30 (16.7)	(5.6, 34.7)	1/17 (5.9)	(0.1, 28.7)
Day 28	7/30 (23.3)	(9.9, 42.3)	3/17 (17.6)	(3.8, 43.4)
Day 49	11/30 (36.7)	(19.9, 56.1)	4/17 (23.5)	(6.8, 49.9)
<b>cUTI</b>	<b>N' = 26</b>		<b>N' = 10</b>	
Day 14	3/26 (11.5)	(2.4, 30.2)	2/10 (20.0)	(2.5, 55.6)
Day 28	4/26 (15.4)	(4.4, 34.9)	2/10 (20.0)	(2.5, 55.6)
Day 49	4/26 (15.4)	(4.4, 34.9)	2/10 (20.0)	(2.5, 55.6)
<b>Overall</b>	<b>N' = 101</b>		<b>N' = 49</b>	
Day 14	19/101 (18.8)	(11.7, 27.8)	6/49 (12.2)	(4.6, 24.8)
Day 28	25/101 (24.8)	(16.7, 34.3)	9/49 (18.4)	(8.8, 32.0)
Day 49	34/101 (33.7)	(24.6, 43.8)	10/49 (20.4)	(10.2, 34.3)

BAT = best available therapy; BSI = bloodstream infection; CI = confidence interval; cUTI = complicated urinary tract infection; HAP = hospital-acquired pneumonia; HCAP = healthcare-associated pneumonia; VAP = ventilator-associated pneumonia

Percentage is calculated using N as the denominator where N is the number of patients who had the specified infection site and continued the study or expired at each time point. The 95% CI is calculated using Clopper-Pearson method

The patients with unknown survival status at Day 49 (i.e, censored before Day 49) are included in the table as a survivor.

**Figure 24** **Kaplan Meier Curve for All Cause Mortality (Safety Population)**



### 10.7.1 Adverse Events Leading to Death

Adverse events leading to death are summarized in Table 37. The most marked difference between groups was in the classification of Infections and Infestations. This was 20.8% (21/101) of patients in the cefiderocol group and 6.1% (3/49) of patients in the BAT group. This difference represents worsening or progressions of infections in critically ill patients.

**Table 37** **CREDIBLE-CR Patients With Adverse Events Leading to Death by System Organ Class and Preferred Term (Safety Population)**

System Organ Class Preferred Term	Cefiderocol n = 101 n (%)	BAT n = 49 n (%)
AEs leading to death	34 (33.7)	9 (18.4)
Cardiac disorders	6 (5.9)	3 (6.1)
Bradycardia	0	1 (2.0)
Cardiac arrest	4 (4.0)	2 (4.1)
Cardiac failure congestive	1 (1.0)	0
Myocardial infarction	1 (1.0)	0
General disorders and administration site conditions	3 (3.0)	3 (6.1)
General physical health deterioration	0	1 (2.0)

<b>System Organ Class Preferred Term</b>	<b>Cefiderocol n = 101 n (%)</b>	<b>BAT n = 49 n (%)</b>
Multi-organ failure	2 (2.0)	2 (4.1)
Sudden death	1 (1.0)	0
Hepatobiliary disorders	2 (2.0)	0
Chronic hepatic failure	1 (1.0)	0
Hepatic failure	1 (1.0)	0
Infections and infestations	21 (20.8)	3 (6.1)
Bacteremia	2 (2.0)	0
Device related infection	0	1 (2.0)
Pneumonia	5 (5.0)	0
Pneumonia bacterial	1 (1.0)	0
Sepsis	3 (3.0)	0
Septic shock	11 (10.9)	3 (6.1)
Metabolism and nutrition disorders	1 (1.0)	1 (2.0)
Hyponatremia	1 (1.0)	0
Metabolic acidosis	0	1 (2.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1.0)	0
Lung neoplasm malignant	1 (1.0)	0
Renal and urinary disorders	3 (3.0)	1 (2.0)
Acute kidney injury	1 (1.0)	1 (2.0)
Anuria	1 (1.0)	0
Oliguria	2 (2.0)	0
Respiratory, thoracic and mediastinal disorders	4 (4.0)	2 (4.1)
Acute respiratory failure	0	1 (2.0)
Obstructive airways disorder	1 (1.0)	0
Pneumonia aspiration	1 (1.0)	0
Respiratory arrest	0	1 (2.0)
Respiratory failure	2 (2.0)	0
Vascular disorders	1 (1.0)	0
Hypotension	1 (1.0)	0
Shock	1 (1.0)	0

AEs, adverse events; BAT, best available therapy.

Percentage is calculated using the number of patients in the column heading as the denominator. AEs that started after the first dose of the study drug and up to End of Study visit are defined as treatment-emergent. Although a patient may have had 2 or more AEs, the patient is counted only once within a System Organ Class category. The same patient may contribute to 2 or more Preferred Terms in the same System Organ Class category.

One patient received Compassionate Use cefiderocol after completion of BAT; this patient is included under BAT in this table.

### 10.7.2 External Blinded Adjudication Committee

When considering death-related clinical trial endpoints, all-cause mortality is usually used, rather than attributable mortality as the former is more easily determined than the latter. Attributable mortality refers to death directly related to a disease, treatment or background condition. Previous examination of infection-attributable death in patients with antibiotic resistant bacterial infections or ventilator associated pneumonia have ranged from 13 to 50%. ([Melsen 2013](#), [Falagas 2014](#)). None of the cefiderocol deaths was considered to be due to an adverse drug reaction by the investigator or Shionogi. However, CREDIBLE-CR was an open label study which could introduce bias as discussed in ([Section 10.1](#)). To introduce a blinded assessment of each of the fatal cases, an external, independent adjudication committee that was blinded to study treatment was convened after the study began to provide an independent assessment of the cause of death. The external blinded adjudication committee consisted of three expert physicians: A Professor of Intensive Care Medicine (UK), a Professor of Medicine and Infectious Diseases (US) and a Professor of Medicine in Pulmonary and Critical Care (US). Importantly, the adjudication members were not informed of any differences in mortality between treatment groups in addition to being blinded to the patient's actual treatment regimen (including susceptibility data). Each member of the adjudication committee first reviewed the detailed patient's medical narrative and chronographic information independently and determined whether the death was in category 1 (not due to original Gram-negative infection) or category 2 (due to original Gram-negative infection). If the vote was split between the 3 members, a discussion took place only among the members and they voted again. The final conclusion was decided by the majority.

If the death was due to the original Gram-negative infection (Category 2), the committee was asked if it was due to a lack of antibiotic effectiveness. If the death was not due to the original Gram-negative infection (Category 1), the committee was asked if it was due to comorbidities, a different infection, an adverse event, or an iatrogenic cause. The committee evaluated the 43 deaths listed in [Table 39](#) (cefiderocol treated patients) and [Table 40](#) (BAT treated patients), which included deaths that occurred after the first dose of the study drug and up to the EOS. This includes deaths that occurred after the EOS visit but were due to a serious adverse event that was continuing at the EOS visit. There were 34 deaths in the cefiderocol-treatment group and 9 in the BAT-treatment group. The categorization of deaths by the adjudication committee is provided in [Table 38](#). The committee assessment was that none of these patients' death was due to a drug related adverse event (Category 1C).

**Table 38 Results of Adjudication Committee Review (Safety Population)**

<b>Category and Subcategory</b>	<b>CFDC n (%)</b>	<b>BAT n (%)</b>
Overall mortality	34 (33.7)	9 (18.4)
<b>1.</b> Death unrelated to Gram-negative study infection for which the patient was randomized into the CREDIBLE-CR study	16 (15.8)	4 (8.2)
<b>1A.</b> Likely due to the patient's underlying comorbidity	10 (9.9)	2 (4.1)
<b>1B.</b> Related to infection other than original Gram-negative infection	4 (4.0)	2 (4.1)
<b>1C.</b> Due to drug-related AE	0	0
<b>1D.</b> Due to iatrogenic cause	0	0
Cases that did not have a unanimous subcategory vote in category 1	2 (2.0)	0
<b>2.</b> Death directly related to the Gram-negative infection for which the patient was randomized into the CREDIBLE-CR study	18 (17.8)	5 (10.2)
<b>Yes.</b> Infection-related death represents a failure of antibiotic treatment	16 (15.8)	4 (8.2)
<b>No.</b> Infection-related death does not represent a failure of antibiotic treatment	1 (1.0)	1 (2.0)
Cases that did not have a unanimous subcategory vote in category 2	1 (1.0)	0

AE, adverse event; BAT, best available therapy; CFDC, cefiderocol.

A list of Patient Profiles of deaths of the cefiderocol treated patients is provided in [Table 39](#) and a list of Patient Profiles of deaths of the BAT treated patients is provided in [Table 40](#). Data include patient demographics, medical history, microbiology, PK and outcomes and are sorted by adjudication committee assessment.

Approximately 50% of the deaths were attributable to the original Gram-negative infection in both the cefiderocol arm and the BAT arm (18/34 and 5/9, respectively).

Detailed narratives of the 18 cefiderocol patients and 5 BAT patients who were adjudicated to Category 2 (infection-attributable mortality) are included in [Appendix 15.7](#).

**Table 39 List of Patient Profiles of Deaths in the CREDIBLE-CR Study (Cefiderocol)**

Patient Age (Years)/Gender Relevant Medical History Baseline CrCl (mL/min) Renal Impairment [a] APACHE II/MELD	Number of Days from Hospital Admission to Randomization  Prior Antibiotic Tx Within 2 Weeks of Randomization (Y/N)  Prior Antibiotic Tx Failure at Randomization (Y/N)	Infection Dx  Baseline Pathogen  MIC (µg/mL)  (% Time Above MIC Plasma/ELF)	Tx Duration	Clinical Outcome at EOT/TOC  Microbiological Outcome at EOT/TOC	Fatal SAE Preferred Term  SAE Onset Day/ Time to SAE from Last Dose (Days)	Cause of Death  Study Day of Death/ Time to Death Since Last Dose (Days)  Adjudication Committee Category
<b>Adjudication Committee Category 1: death not directly related to the Gram-negative infection for which the patient was randomized</b>  1-A: likely due to the patient's underlying comorbidity 1-B: related to infection other than the original Gram –negative infection 1-C: due to drug-related adverse event 1-D: due to iatrogenic cause  1: cases that did not have a unanimous subcategory vote in Category 1						
Patient # 01  54/M  Epilepsy, spinal cord injury, paraplegia, craniocerebral injury  71.9  Mild  2/6.4	5  N  N	Sepsis (sacral ulcer)  <i>Pseudomonas aeruginosa</i>  MIC: 0.5  (Plasma 100%)	22 days	Cure/cure  Indeterminate/ indeterminate	Sudden death  43/21	Cardio-respiratory arrest that lead to sudden death  43/21  1-A

<b>Patient</b>  <b>Age (Years)/Gender</b>  <b>Relevant Medical History</b>  <b>Baseline CrCl (mL/min)</b>  <b>Renal Impairment [a]</b>  <b>APACHE II/MELD</b>	<b>Number of Days from Hospital Admission to Randomization</b>  <b>Prior Antibiotic Tx Within 2 Weeks of Randomization (Y/N)</b>  <b>Prior Antibiotic Tx Failure at Randomization (Y/N)</b>	<b>Infection Dx</b>  <b>Baseline Pathogen</b>  <b>MIC (µg/mL)</b>  <b>(% Time Above MIC Plasma/ELF)</b>	<b>Tx Duration</b>	<b>Clinical Outcome at EOT/TOC</b>  <b>Microbiological Outcome at EOT/TOC</b>	<b>Fatal SAE Preferred Term</b>  <b>SAE Onset Day/ Time to SAE from Last Dose (Days)</b>	<b>Cause of Death</b>  <b>Study Day of Death/ Time to Death Since Last Dose (Days)</b>  <b>Adjudication Committee Category</b>
Patient # 02  83/M  Diabetes mellitus, chronic renal failure, arterial hypertension  22.4  Severe  20/23	9  Y  N	cUTI  No baseline pathogen detected  NA  (NA)	5 days	Indeterminate/indeterminate	Oliguria, anuria  4/-1	Progression of renal failure (study participation revoked and minimal intervention requested)  7/2  1-A
Patient # 03  46/M  Type 2 diabetes mellitus, hepatic failure, nosocomial pneumonia, septic shock  179.0  ARC  13/17.2	9  Y  Y	HAP  <i>Klebsiella oxytoca</i> , <i>Klebsiella pneumoniae</i>  MIC: 0.06/0.25  (Plasma 100%/ ELF 100% )	9 days	Failure/cure  Persistence/indeterminate	Chronic hepatic failure  2/-7	Refractory hepatic failure  35/26  1-A

<b>Patient</b> <b>Age (Years)/Gender</b> <b>Relevant Medical History</b> <b>Baseline CrCl (mL/min)</b> <b>Renal Impairment [a]</b> <b>APACHE II/MELD</b>	<b>Number of Days from Hospital Admission to Randomization</b> <b>Prior Antibiotic Tx Within 2 Weeks of Randomization (Y/N)</b> <b>Prior Antibiotic Tx Failure at Randomization (Y/N)</b>	<b>Infection Dx</b> <b>Baseline Pathogen</b> <b>MIC (µg/mL)</b> <b>(% Time Above MIC Plasma/ELF)</b>	<b>Tx Duration</b>	<b>Clinical Outcome at EOT/TOC</b> <b>Microbiological Outcome at EOT/TOC</b>	<b>Fatal SAE Preferred Term</b> <b>SAE Onset Day/ Time to SAE from Last Dose (Days)</b>	<b>Cause of Death</b> <b>Study Day of Death/ Time to Death Since Last Dose (Days)</b> <b>Adjudication Committee Category</b>
Patient # 04 70/M Diabetes mellitus, ischaemic cardiomyopathy, COPD, cardiac failure, respiratory failure 81.8 Normal 15/8.1	33 Y N	VAP <i>Stenotrophomonas maltophilia</i> MIC: < 0.03 (Plasma 100%/ ELF 100%)	11 days	Cure/ indeterminate Eradication/ indeterminate	Myocardial infarction 12/1	Cardiogenic shock secondary to myocardial infarct 13/2 1-A

<b>Patient</b> <b>Age (Years)/Gender</b> <b>Relevant Medical History</b> <b>Baseline CrCl (mL/min)</b> <b>Renal Impairment [a]</b> <b>APACHE II/MELD</b>	<b>Number of Days from Hospital Admission to Randomization</b>  <b>Prior Antibiotic Tx Within 2 Weeks of Randomization (Y/N)</b>  <b>Prior Antibiotic Tx Failure at Randomization (Y/N)</b>	<b>Infection Dx</b>  <b>Baseline Pathogen</b>  <b>MIC (µg/mL)</b>  <b>(% Time Above MIC Plasma/ELF)</b>	<b>Tx Duration</b>	<b>Clinical Outcome at EOT/TOC</b>  <b>Microbiological Outcome at EOT/TOC</b>	<b>Fatal SAE Preferred Term</b>  <b>SAE Onset Day/ Time to SAE from Last Dose (Days)</b>	<b>Cause of Death</b>  <b>Study Day of Death/ Time to Death Since Last Dose (Days)</b>  <b>Adjudication Committee Category</b>
Patient # 05 24/F Trauma with head, lung, and abdominal injuries; traumatic skull fracture; acute respiratory failure; traumatic liver injury; cerebral haemorrhage; bacteraemia 184.9 ARC 12/12.4	10 Y N	BSI <i>Acinetobacter baumannii</i> MIC: 0.12 (NA)	2 days	Failure/failure Indeterminate/ indeterminate	Hyponatremia 2/0	Multiple trauma and skull fracture (declared brain dead, life support withdrawn) 6/4 1-A

<b>Patient</b> <b>Age (Years)/Gender</b> <b>Relevant Medical History</b> <b>Baseline CrCl (mL/min)</b> <b>Renal Impairment [a]</b> <b>APACHE II/MELD</b>	<b>Number of Days from Hospital Admission to Randomization</b>  <b>Prior Antibiotic Tx Within 2 Weeks of Randomization (Y/N)</b>  <b>Prior Antibiotic Tx Failure at Randomization (Y/N)</b>	<b>Infection Dx</b>  <b>Baseline Pathogen</b>  <b>MIC (µg/mL)</b>  <b>(% Time Above MIC Plasma/ELF)</b>	<b>Tx Duration</b>	<b>Clinical Outcome at EOT/TOC</b>  <b>Microbiological Outcome at EOT/TOC</b>	<b>Fatal SAE Preferred Term</b>  <b>SAE Onset Day/ Time to SAE from Last Dose (Days)</b>	<b>Cause of Death</b>  <b>Study Day of Death/ Time to Death Since Last Dose (Days)</b>  <b>Adjudication Committee Category</b>
Patient # 06  79/M  Radical cystectomy for bladder, intestinal perforation, sepsis  41.3  Moderate  17/missing	85  Y  Y	BSI  <i>Klebsiella pneumoniae</i>  MIC:2.0  (NA)	3 days	Failure/failure  Indeterminate/ indeterminate	Cardiac arrest  3/0	Cardiac arrest  3/0  1-A

<b>Patient</b> <b>Age (Years)/Gender</b> <b>Relevant Medical History</b> <b>Baseline CrCl (mL/min)</b> <b>Renal Impairment [a]</b> <b>APACHE II/MELD</b>	<b>Number of Days from Hospital Admission to Randomization</b> <b>Prior Antibiotic Tx Within 2 Weeks of Randomization (Y/N)</b> <b>Prior Antibiotic Tx Failure at Randomization (Y/N)</b>	<b>Infection Dx</b> <b>Baseline Pathogen</b> <b>MIC (µg/mL)</b> <b>(% Time Above MIC Plasma/ELF)</b>	<b>Tx Duration</b>	<b>Clinical Outcome at EOT/TOC</b> <b>Microbiological Outcome at EOT/TOC</b>	<b>Fatal SAE Preferred Term</b> <b>SAE Onset Day/ Time to SAE from Last Dose (Days)</b>	<b>Cause of Death</b> <b>Study Day of Death/ Time to Death Since Last Dose (Days)</b> <b>Adjudication Committee Category</b>
Patient # 07 84/M Congestive heart failure (NYHA: 4; EF: 15-20%), suspected malignant mesothelioma per CT, COPD, pneumonia, acute on chronic renal failure 31.2 Moderate 18/13.6	5 Y N	BSI <i>Acinetobacter baumannii</i> MIC: NA (NA)	21 days	Cure/cure Eradication/eradication	Lung neoplasm malignant 2/-19 Cardiac failure congestive 35/14	Congestive heart failure exacerbation 35/14 1-A

<b>Patient</b>  <b>Age (Years)/Gender</b>  <b>Relevant Medical History</b>  <b>Baseline CrCl (mL/min)</b>  <b>Renal Impairment [a]</b>  <b>APACHE II/MELD</b>	<b>Number of Days from Hospital Admission to Randomization</b>  <b>Prior Antibiotic Tx Within 2 Weeks of Randomization (Y/N)</b>  <b>Prior Antibiotic Tx Failure at Randomization (Y/N)</b>	<b>Infection Dx</b>  <b>Baseline Pathogen</b>  <b>MIC (µg/mL)</b>  <b>(% Time Above MIC Plasma/ELF)</b>	<b>Tx Duration</b>	<b>Clinical Outcome at EOT/TOC</b>  <b>Microbiological Outcome at EOT/TOC</b>	<b>Fatal SAE Preferred Term</b>  <b>SAE Onset Day/ Time to SAE from Last Dose (Days)</b>	<b>Cause of Death</b>  <b>Study Day of Death/ Time to Death Since Last Dose (Days)</b>  <b>Adjudication Committee Category</b>
Patient # 08  66/F  Ocular lymphoma, liver cirrhosis, bronchiectasis, respiratory failure, acute kidney injury  71.0  Mild  28/9.8	53  Y  Y	VAP  <i>Acinetobacter baumannii</i> , <i>Pseudomonas aeruginosa</i>  MIC:2/0.12  (Plasma 100%/ ELF 100%)	15 days	Cure/failure  Persistence/ persistence	Septic shock  21/6	Septic shock  45/30  1-A

<b>Patient</b>  <b>Age (Years)/Gender</b>  <b>Relevant Medical History</b>  <b>Baseline CrCl (mL/min)</b>  <b>Renal Impairment [a]</b>  <b>APACHE II/MELD</b>	<b>Number of Days from Hospital Admission to Randomization</b>  <b>Prior Antibiotic Tx Within 2 Weeks of Randomization (Y/N)</b>  <b>Prior Antibiotic Tx Failure at Randomization (Y/N)</b>	<b>Infection Dx</b>  <b>Baseline Pathogen</b>  <b>MIC (µg/mL)</b>  <b>(% Time Above MIC Plasma/ELF)</b>	<b>Tx Duration</b>	<b>Clinical Outcome at EOT/TOC</b>  <b>Microbiological Outcome at EOT/TOC</b>	<b>Fatal SAE Preferred Term</b>  <b>SAE Onset Day/ Time to SAE from Last Dose (Days)</b>	<b>Cause of Death</b>  <b>Study Day of Death/ Time to Death Since Last Dose (Days)</b>  <b>Adjudication Committee Category</b>
Patient # 09  86/F  Chronic kidney disease, urosepsis, asystole, HAP, continuous renal replacement therapy  79.7  Mild  24/25.1	35  Y  Y	HAP  <i>Acinetobacter baumannii</i>  MIC:0.06  (Plasma 100%/ ELF 100%)	5 days	Indeterminate/ indeterminate  Indeterminate/ indeterminate	Acute kidney injury  5/0	AKI aggravation (continuous renal replacement therapy stopped due to financial reasons)  5/0  1-A

<b>Patient</b> <b>Age (Years)/Gender</b> <b>Relevant Medical History</b> <b>Baseline CrCl (mL/min)</b> <b>Renal Impairment [a]</b> <b>APACHE II/MELD</b>	<b>Number of Days from Hospital Admission to Randomization</b> <b>Prior Antibiotic Tx Within 2 Weeks of Randomization (Y/N)</b> <b>Prior Antibiotic Tx Failure at Randomization (Y/N)</b>	<b>Infection Dx</b> <b>Baseline Pathogen</b> <b>MIC (µg/mL)</b> <b>(% Time Above MIC Plasma/ELF)</b>	<b>Tx Duration</b>	<b>Clinical Outcome at EOT/TOC</b> <b>Microbiological Outcome at EOT/TOC</b>	<b>Fatal SAE Preferred Term</b> <b>SAE Onset Day/ Time to SAE from Last Dose (Days)</b>	<b>Cause of Death</b> <b>Study Day of Death/ Time to Death Since Last Dose (Days)</b> <b>Adjudication Committee Category</b>
Patient # 10 82/M Gangrenous cholecystitis, pneumonia, septic shock, acute kidney injury 46.5 Moderate 23/11	34 Y Y	Sepsis <i>Acinetobacter baumannii</i> MIC: 2.0 (Plasma 100%)	9 days	Cure/cure Eradication/persistence	Obstructive airways disorder 27/18	Obstructive airways disorder 27/18 1-A
Patient # 11 70/F Hyperlipidaemia, diabetes mellitus, renal failure, toxic epidermal necrolysis, sepsis 33.2 Moderate 14/14.9	3 Y N	BSI <i>Acinetobacter baumannii</i> MIC: 0.25 (Plasma 100%)	14 days	Cure/failure Eradication/indeterminate	Cardiac arrest 19/5	Cardiac arrest 19/5 1-B

<b>Patient</b> <b>Age (Years)/Gender</b> <b>Relevant Medical History</b> <b>Baseline CrCl (mL/min)</b> <b>Renal Impairment [a]</b> <b>APACHE II/MELD</b>	<b>Number of Days from Hospital Admission to Randomization</b>  <b>Prior Antibiotic Tx Within 2 Weeks of Randomization (Y/N)</b>  <b>Prior Antibiotic Tx Failure at Randomization (Y/N)</b>	<b>Infection Dx</b>  <b>Baseline Pathogen</b>  <b>MIC (µg/mL)</b>  <b>(% Time Above MIC Plasma/ELF)</b>	<b>Tx Duration</b>	<b>Clinical Outcome at EOT/TOC</b>  <b>Microbiological Outcome at EOT/TOC</b>	<b>Fatal SAE Preferred Term</b>  <b>SAE Onset Day/ Time to SAE from Last Dose (Days)</b>	<b>Cause of Death</b>  <b>Study Day of Death/ Time to Death Since Last Dose (Days)</b>  <b>Adjudication Committee Category</b>
Patient # 12  70/M  Transitional cell carcinoma of bladder, urosepsis, acute kidney injury, mechanical ventilation  13.2  Severe  18/21.5	15  Y  N	BSI  <i>Klebsiella pneumoniae</i>  MIC:2  (NA)	22 days	Failure/failure  Eradication/ indeterminate	Bacteraemia  43/21	Bacteremia, bladder cancer  48/26  1-B

<b>Patient</b> <b>Age (Years)/Gender</b> <b>Relevant Medical History</b> <b>Baseline CrCl (mL/min)</b> <b>Renal Impairment [a]</b> <b>APACHE II/MELD</b>	<b>Number of Days from Hospital Admission to Randomization</b> <b>Prior Antibiotic Tx Within 2 Weeks of Randomization (Y/N)</b> <b>Prior Antibiotic Tx Failure at Randomization (Y/N)</b>	<b>Infection Dx</b> <b>Baseline Pathogen</b> <b>MIC (µg/mL)</b> <b>(% Time Above MIC Plasma/ELF)</b>	<b>Tx Duration</b>	<b>Clinical Outcome at EOT/TOC</b> <b>Microbiological Outcome at EOT/TOC</b>	<b>Fatal SAE Preferred Term</b> <b>SAE Onset Day/ Time to SAE from Last Dose (Days)</b>	<b>Cause of Death</b> <b>Study Day of Death/ Time to Death Since Last Dose (Days)</b> <b>Adjudication Committee Category</b>
Patient # 13 47/F Cholangiocarcinoma, gall bladder cancer, bacteraemia, disseminated intravascular coagulation 94.4 Normal 14/22	25 Y Y	BSI <i>Klebsiella pneumoniae</i> MIC: 1.0 (Plasma 100%)	9 days	Indeterminate/ indeterminate Indeterminate/ indeterminate	Septic shock 9/0	Septic shock 9/0 1-B

<b>Patient</b>  <b>Age (Years)/Gender</b>  <b>Relevant Medical History</b>  <b>Baseline CrCl (mL/min)</b>  <b>Renal Impairment [a]</b>  <b>APACHE II/MELD</b>	<b>Number of Days from Hospital Admission to Randomization</b>  <b>Prior Antibiotic Tx Within 2 Weeks of Randomization (Y/N)</b>  <b>Prior Antibiotic Tx Failure at Randomization (Y/N)</b>	<b>Infection Dx</b>  <b>Baseline Pathogen</b>  <b>MIC (µg/mL)</b>  <b>(% Time Above MIC Plasma/ELF)</b>	<b>Tx Duration</b>	<b>Clinical Outcome at EOT/TOC</b>  <b>Microbiological Outcome at EOT/TOC</b>	<b>Fatal SAE Preferred Term</b>  <b>SAE Onset Day/ Time to SAE from Last Dose (Days)</b>	<b>Cause of Death</b>  <b>Study Day of Death/ Time to Death Since Last Dose (Days)</b>  <b>Adjudication Committee Category</b>
Patient # 14  78/M  Progressive dyspnea, non- small cell lung cancer, brain/liver metastases, COPD  80.3  Normal  19/7.2	26  Y  Y	VAP  <i>Acinetobacter baumannii</i> , <i>Stenotrophomonas maltophilia</i>  MIC: 1/0.25  (Plasma 100%/ ELF 100%)	10 days	Failure/failure  Persistence/ indeterminate	Respiratory failure  10/0  Septic shock  10/0	Hypoxic respiratory failure, septic shock  19/9  1-B

<b>Patient</b> <b>Age (Years)/Gender</b> <b>Relevant Medical History</b> <b>Baseline CrCl (mL/min)</b> <b>Renal Impairment [a]</b> <b>APACHE II/MELD</b>	<b>Number of Days from Hospital Admission to Randomization</b> <b>Prior Antibiotic Tx Within 2 Weeks of Randomization (Y/N)</b> <b>Prior Antibiotic Tx Failure at Randomization (Y/N)</b>	<b>Infection Dx</b> <b>Baseline Pathogen</b> <b>MIC (µg/mL)</b> <b>(% Time Above MIC Plasma/ELF)</b>	<b>Tx Duration</b>	<b>Clinical Outcome at EOT/TOC</b> <b>Microbiological Outcome at EOT/TOC</b>	<b>Fatal SAE Preferred Term</b> <b>SAE Onset Day/ Time to SAE from Last Dose (Days)</b>	<b>Cause of Death</b> <b>Study Day of Death/ Time to Death Since Last Dose (Days)</b> <b>Adjudication Committee Category</b>
Patient # 15 77/M Diabetes mellitus, cerebrovascular accident, neurogenic bladder 59.2 Mild 6/8.1	4 Y Y	cUTI No baseline pathogen detected MIC: 1.0 (NA)	12 days	Cure/ indeterminate	Pneumonia aspiration 17/5	Pneumonia aspiration 25/13 1

<b>Patient</b> <b>Age (Years)/Gender</b> <b>Relevant Medical History</b> <b>Baseline CrCl (mL/min)</b> <b>Renal Impairment [a]</b> <b>APACHE II/MELD</b>	<b>Number of Days from Hospital Admission to Randomization</b> <b>Prior Antibiotic Tx Within 2 Weeks of Randomization (Y/N)</b> <b>Prior Antibiotic Tx Failure at Randomization (Y/N)</b>	<b>Infection Dx</b> <b>Baseline Pathogen</b> <b>MIC (µg/mL)</b> <b>(% Time Above MIC Plasma/ELF)</b>	<b>Tx Duration</b>	<b>Clinical Outcome at EOT/TOC</b> <b>Microbiological Outcome at EOT/TOC</b>	<b>Fatal SAE Preferred Term</b> <b>SAE Onset Day/ Time to SAE from Last Dose (Days)</b>	<b>Cause of Death</b> <b>Study Day of Death/ Time to Death Since Last Dose (Days)</b> <b>Adjudication Committee Category</b>
Patient # 16 77/M Haemorrhage intracranial, HAP, septic shock 10.2 Severe 29/23.3	33 Y Y	BSI <i>Klebsiella pneumoniae</i> MIC:1.0 (Plasma 100%)	8 days	Cure/cure Eradication/eradication	Sepsis 25/17	Sepsis 36/28 1

Patient Age (Years)/Gender Relevant Medical History Baseline CrCl (mL/min) Renal Impairment [a] APACHE II/MELD	Number of Days from Hospital Admission to Randomization  Prior Antibiotic Tx Within 2 Weeks of Randomization (Y/N)  Prior Antibiotic Tx Failure at Randomization (Y/N)	Infection Dx  Baseline Pathogen  MIC (µg/mL)  (% Time Above MIC Plasma/ELF)	Tx Duration	Clinical Outcome at EOT/TOC  Microbiological Outcome at EOT/TOC	Fatal SAE Preferred Term  SAE Onset Day/ Time to SAE from Last Dose (Days)	Cause of Death  Study Day of Death/ Time to Death Since Last Dose (Days)  Adjudication Committee Category
<p><b>Adjudication Committee Category 2: death directly related to the Gram-negative infection for which the patient was randomized</b></p> <p>2-Yes: infection-related death represent a failure of antibiotic treatment 2-No: infection-related death does not represent a failure of antibiotic treatment 2: cases that did not have a unanimous subcategory vote in Category 2</p>						
<p>Patient # 17</p> <p>92/M</p> <p>COPD, ischaemic cardiomyopathy, transient ischemic attack</p> <p>35.6</p> <p>Moderate</p> <p>11/9.7</p>	<p>2</p> <p>Y</p> <p>N</p>	<p>cUTI</p> <p><i>Klebsiella pneumoniae</i></p> <p>MIC: 1.0 (Plasma 100%)</p>	<p>4 days</p>	<p>Indeterminate/ indeterminate</p> <p>Indeterminate/ indeterminate</p>	<p>Hypotension, oliguria, multiple organ dysfunction syndrome, shock</p> <p>3/-1</p>	<p>Refractory shock of undetermined origin (family asked for no intensive care admission)</p> <p>4/0</p> <p>2-Yes</p>

<b>Patient</b> <b>Age (Years)/Gender</b> <b>Relevant Medical History</b> <b>Baseline CrCl (mL/min)</b> <b>Renal Impairment [a]</b> <b>APACHE II/MELD</b>	<b>Number of Days from Hospital Admission to Randomization</b> <b>Prior Antibiotic Tx Within 2 Weeks of Randomization (Y/N)</b> <b>Prior Antibiotic Tx Failure at Randomization (Y/N)</b>	<b>Infection Dx</b> <b>Baseline Pathogen</b> <b>MIC (µg/mL)</b> <b>(% Time Above MIC Plasma/ELF)</b>	<b>Tx Duration</b>	<b>Clinical Outcome at EOT/TOC</b> <b>Microbiological Outcome at EOT/TOC</b>	<b>Fatal SAE Preferred Term</b> <b>SAE Onset Day/ Time to SAE from Last Dose (Days)</b>	<b>Cause of Death</b> <b>Study Day of Death/ Time to Death Since Last Dose (Days)</b> <b>Adjudication Committee Category</b>
<b>Patient # 18</b> 78/M Aortic aneurysm rupture, abnormal liver function, acute renal failure 32.9 Moderate 17/28	12 Y Y	HAP <i>Acinetobacter baumannii</i> , <i>Escherichia coli</i> , <i>Klebsiella pneumoniae</i> MIC: 0.5/0.06/0.25 (Plasma 100%/ ELF 100%)	14 days	Cure/failure Persistence/persistence	Septic shock 29/15	Septic shock-multiple organ failure 31/17 2-Yes

Patient Age (Years)/Gender Relevant Medical History Baseline CrCl (mL/min) Renal Impairment [a] APACHE II/MELD	Number of Days from Hospital Admission to Randomization Prior Antibiotic Tx Within 2 Weeks of Randomization (Y/N) Prior Antibiotic Tx Failure at Randomization (Y/N)	Infection Dx Baseline Pathogen MIC (µg/mL) (% Time Above MIC Plasma/ELF)	Tx Duration	Clinical Outcome at EOT/TOC Microbiological Outcome at EOT/TOC	Fatal SAE Preferred Term SAE Onset Day/ Time to SAE from Last Dose (Days)	Cause of Death Study Day of Death/ Time to Death Since Last Dose (Days) Adjudication Committee Category
<a href="#">Patient # 19</a> 64/F Chronic respiratory failure, bronchopulmonary aspergillosis, allergic tracheobronchitis 104.7 Normal 13/7	19 Y N	BSI <i>Acinetobacter  baumannii</i> MIC:0.12 (Plasma 100%)	9 days	Failure/failure Indeterminate/ indeterminate	Septic shock 8/-1	Septic shock 11/2 2-Yes

<b>Patient</b>  <b>Age (Years)/Gender</b>  <b>Relevant Medical History</b>  <b>Baseline CrCl (mL/min)</b>  <b>Renal Impairment [a]</b>  <b>APACHE II/MELD</b>	<b>Number of Days from Hospital Admission to Randomization</b>  <b>Prior Antibiotic Tx Within 2 Weeks of Randomization (Y/N)</b>  <b>Prior Antibiotic Tx Failure at Randomization (Y/N)</b>	<b>Infection Dx</b>  <b>Baseline Pathogen</b>  <b>MIC (µg/mL)</b>  <b>(% Time Above MIC Plasma/ELF)</b>	<b>Tx Duration</b>	<b>Clinical Outcome at EOT/TOC</b>  <b>Microbiological Outcome at EOT/TOC</b>	<b>Fatal SAE Preferred Term</b>  <b>SAE Onset Day/ Time to SAE from Last Dose (Days)</b>	<b>Cause of Death</b>  <b>Study Day of Death/ Time to Death Since Last Dose (Days)</b>  <b>Adjudication Committee Category</b>
<b>Patient # 20</b>  68/M  Adenocarcinoma of the esophagus metastatic, pulmonary emphysema, hypertrophic cardiomyopathy, chronic kidney disease  44.1  Moderate  18/15.8	5  N  N	Sepsis (initial dx) HAP (final dx)  <i>Enterobacter cloacae</i>  MIC: 16  (plasma 100%/ ELF 0%)	6 days	Failure/failure  Indeterminate/ indeterminate	Respiratory failure  12/6	Deterioration of respiratory function  (limitation of care decided by family and medical staff)  12/6  2-Yes

<b>Patient</b>  <b>Age (Years)/Gender</b>  <b>Relevant Medical History</b>  <b>Baseline CrCl (mL/min)</b>  <b>Renal Impairment [a]</b>  <b>APACHE II/MELD</b>	<b>Number of Days from Hospital Admission to Randomization</b>  <b>Prior Antibiotic Tx Within 2 Weeks of Randomization (Y/N)</b>  <b>Prior Antibiotic Tx Failure at Randomization (Y/N)</b>	<b>Infection Dx</b>  <b>Baseline Pathogen</b>  <b>MIC (µg/mL)</b>  <b>(% Time Above MIC Plasma/ELF)</b>	<b>Tx Duration</b>	<b>Clinical Outcome at EOT/TOC</b>  <b>Microbiological Outcome at EOT/TOC</b>	<b>Fatal SAE Preferred Term</b>  <b>SAE Onset Day/ Time to SAE from Last Dose (Days)</b>	<b>Cause of Death</b>  <b>Study Day of Death/ Time to Death Since Last Dose (Days)</b>  <b>Adjudication Committee Category</b>
<b>Patient # 21</b>  29/F  Metastatic rectal cancer (liver, lungs, brain, arm), malnutrition, acute kidney injury, dyspnoea  539.6  ARC  24/10	6  Y  N	BSI  <i>Acinetobacter baumannii</i>  MIC: 0.06  (Plasma 100%)	6 days	Failure/failure  Indeterminate/ indeterminate	Cardiac arrest  6/0  Septic shock  5/-1	Septic shock  6/0  2-Yes

<b>Patient</b>  <b>Age (Years)/Gender</b>  <b>Relevant Medical History</b>  <b>Baseline CrCl (mL/min)</b>  <b>Renal Impairment [a]</b>  <b>APACHE II/MELD</b>	<b>Number of Days from Hospital Admission to Randomization</b>  <b>Prior Antibiotic Tx Within 2 Weeks of Randomization (Y/N)</b>  <b>Prior Antibiotic Tx Failure at Randomization (Y/N)</b>	<b>Infection Dx</b>  <b>Baseline Pathogen</b>  <b>MIC (µg/mL)</b>  <b>(% Time Above MIC Plasma/ELF)</b>	<b>Tx Duration</b>	<b>Clinical Outcome at EOT/TOC</b>  <b>Microbiological Outcome at EOT/TOC</b>	<b>Fatal SAE Preferred Term</b>  <b>SAE Onset Day/ Time to SAE from Last Dose (Days)</b>	<b>Cause of Death</b>  <b>Study Day of Death/ Time to Death Since Last Dose (Days)</b>  <b>Adjudication Committee Category</b>
<b>Patient # 22</b>  69/M  Pulmonary haemorrhage (iatrogenic), hemothorax, septic shock  73.7  Mild  13/23.9	17  Y  Y	VAP  <i>Acinetobacter baumannii</i>  MIC:1  (NA)	9 days	Failure/failure  Indeterminate/ indeterminate	Sepsis  9/0	Non resolved sepsis  9/0  2-Yes
<b>Patient # 23</b>  65/M  Lung adenocarcinoma, esophagus perforation, mediastinitis, septic shock  26.9  Severe  27/15.6	63  Y  Y	VAP  <i>Acinetobacter baumannii</i> , <i>Pseudomonas aeruginosa</i>  MIC: 0.5/1  (Plasma 100%/ ELF 100%)	11 days	Failure/failure  Persistence/ indeterminate	Sepsis  13/2	Sepsis  13/2  2-Yes

<b>Patient</b> <b>Age (Years)/Gender</b> <b>Relevant Medical History</b> <b>Baseline CrCl (mL/min)</b> <b>Renal Impairment [a]</b> <b>APACHE II/MELD</b>	<b>Number of Days from Hospital Admission to Randomization</b>  <b>Prior Antibiotic Tx Within 2 Weeks of Randomization (Y/N)</b>  <b>Prior Antibiotic Tx Failure at Randomization (Y/N)</b>	<b>Infection Dx</b>  <b>Baseline Pathogen</b>  <b>MIC (µg/mL)</b>  <b>(% Time Above MIC Plasma/ELF)</b>	<b>Tx Duration</b>	<b>Clinical Outcome at EOT/TOC</b>  <b>Microbiological Outcome at EOT/TOC</b>	<b>Fatal SAE Preferred Term</b>  <b>SAE Onset Day/ Time to SAE from Last Dose (Days)</b>	<b>Cause of Death</b>  <b>Study Day of Death/ Time to Death Since Last Dose (Days)</b>  <b>Adjudication Committee Category</b>
<b>Patient # 24</b>  65/M  Leukocytoclastic vasculitis, necrotic skin ulcers, septic shock, respiratory failure, renal failure  54.8  Mild  24/21.7	9  Y  Y	HAP  <i>Acinetobacter baumannii</i>  MIC: ≤ 0.03  (NA)	14 days	Failure/failure  Persistence/ indeterminate	Pneumonia Acinetobacter  10/-4	Deterioration of <i>Acinetobacter</i> pneumonia  14/0  2-Yes

Patient Age (Years)/Gender Relevant Medical History Baseline CrCl (mL/min) Renal Impairment [a] APACHE II/MELD	Number of Days from Hospital Admission to Randomization  Prior Antibiotic Tx Within 2 Weeks of Randomization (Y/N)  Prior Antibiotic Tx Failure at Randomization (Y/N)	Infection Dx  Baseline Pathogen  MIC (µg/mL)  (% Time Above MIC Plasma/ELF)	Tx Duration	Clinical Outcome at EOT/TOC  Microbiological Outcome at EOT/TOC	Fatal SAE Preferred Term  SAE Onset Day/ Time to SAE from Last Dose (Days)	Cause of Death  Study Day of Death/ Time to Death Since Last Dose (Days)  Adjudication Committee Category
<a href="#">Patient # 25</a> 45/M Severe burns on face and body (petrol bomb), smoke inhalation, acute respiratory failure, acute renal failure  27.7 Severe 19/24.6	41 Y N	VAP  <i>Acinetobacter  baumannii</i>  MIC: 0.25  (NA)	19 days	Failure/failure  Persistence/persistence	Septic shock  38/19	Septic shock  39/20  2-Yes

<b>Patient</b> <b>Age (Years)/Gender</b> <b>Relevant Medical History</b> <b>Baseline CrCl (mL/min)</b> <b>Renal Impairment [a]</b> <b>APACHE II/MELD</b>	<b>Number of Days from Hospital Admission to Randomization</b>  <b>Prior Antibiotic Tx Within 2 Weeks of Randomization (Y/N)</b>  <b>Prior Antibiotic Tx Failure at Randomization (Y/N)</b>	<b>Infection Dx</b>  <b>Baseline Pathogen</b>  <b>MIC (µg/mL)</b>  <b>(% Time Above MIC Plasma/ELF)</b>	<b>Tx Duration</b>	<b>Clinical Outcome at EOT/TOC</b>  <b>Microbiological Outcome at EOT/TOC</b>	<b>Fatal SAE Preferred Term</b>  <b>SAE Onset Day/ Time to SAE from Last Dose (Days)</b>	<b>Cause of Death</b>  <b>Study Day of Death/ Time to Death Since Last Dose (Days)</b>  <b>Adjudication Committee Category</b>
<b>Patient # 26</b>  64/M  Peripheral vascular disease (graft surgery), cardiac arrest, acute renal failure  22.1  Severe  29/28.3	16  Y  Y	HAP  <i>Acinetobacter baumannii</i>  MIC: 0.25  (NA)	4 days	Indeterminate/ indeterminate  Indeterminate/ indeterminate	Septic shock  4/0	Septic shock  4/0  2-Yes

Patient Age (Years)/Gender Relevant Medical History Baseline CrCl (mL/min) Renal Impairment [a] APACHE II/MELD	Number of Days from Hospital Admission to Randomization  Prior Antibiotic Tx Within 2 Weeks of Randomization (Y/N)  Prior Antibiotic Tx Failure at Randomization (Y/N)	Infection Dx  Baseline Pathogen  MIC (µg/mL)  (% Time Above MIC Plasma/ELF)	Tx Duration	Clinical Outcome at EOT/TOC  Microbiological Outcome at EOT/TOC	Fatal SAE Preferred Term  SAE Onset Day/ Time to SAE from Last Dose (Days)	Cause of Death  Study Day of Death/ Time to Death Since Last Dose (Days)  Adjudication Committee Category
<a href="#">Patient # 27</a> 47/M Hepatic cirrhosis, spontaneous bacterial peritonitis, upper gastrointestinal haemorrhage, bacteraemia, fungaemia, septic shock, hepatic encephalopathy, metabolic acidosis 77.5 Mild 9/38.2	5 Y Y	VAP <i>Acinetobacter</i> <i>nosocomialis</i> , <i>Chryseobacterium</i> <i>indolgenes</i> , <i>Pseudomonas</i> <i>aeruginosa</i> , <i>Stenotrophomonas</i> <i>maltophilia</i> MIC: 64/0.5/0.12/0.06 (Plasma 100%/ ELF 0% <i>Acinetobacter</i> , 100% others)	8 days	Failure/ indeterminate  Persistence/ indeterminate	Septic shock 5/-3 Hepatic failure 1/-7	Worsening liver failure, worsening septic shock (DNR palliative extubation) 8/0 2-Yes

<b>Patient</b>  <b>Age (Years)/Gender</b>  <b>Relevant Medical History</b>  <b>Baseline CrCl (mL/min)</b>  <b>Renal Impairment [a]</b>  <b>APACHE II/MELD</b>	<b>Number of Days from Hospital Admission to Randomization</b>  <b>Prior Antibiotic Tx Within 2 Weeks of Randomization (Y/N)</b>  <b>Prior Antibiotic Tx Failure at Randomization (Y/N)</b>	<b>Infection Dx</b>  <b>Baseline Pathogen</b>  <b>MIC (µg/mL)</b>  <b>(% Time Above MIC Plasma/ELF)</b>	<b>Tx Duration</b>	<b>Clinical Outcome at EOT/TOC</b>  <b>Microbiological Outcome at EOT/TOC</b>	<b>Fatal SAE Preferred Term</b>  <b>SAE Onset Day/ Time to SAE from Last Dose (Days)</b>	<b>Cause of Death</b>  <b>Study Day of Death/ Time to Death Since Last Dose (Days)</b>  <b>Adjudication Committee Category</b>
<a href="#">Patient # 28</a>  71/F  Lung adenocarcinoma (stage IV, lobectomy), ARDS, septic shock  52.8  Mild  23/7.4	21  Y  Y	VAP  <i>Acinetobacter nosocomialis</i>  MIC: 0.5  (NA)	3 days	Failure/failure  Indeterminate/ indeterminate	Multiple organ dysfunction syndrome, pneumonia  2/-1	Multiple organ failure, aggravation of VAP  3/0  2-Yes

Patient Age (Years)/Gender Relevant Medical History Baseline CrCl (mL/min) Renal Impairment [a] APACHE II/MELD	Number of Days from Hospital Admission to Randomization  Prior Antibiotic Tx Within 2 Weeks of Randomization (Y/N)  Prior Antibiotic Tx Failure at Randomization (Y/N)	Infection Dx  Baseline Pathogen  MIC (µg/mL)  (% Time Above MIC Plasma/ELF)	Tx Duration	Clinical Outcome at EOT/TOC  Microbiological Outcome at EOT/TOC	Fatal SAE Preferred Term  SAE Onset Day/ Time to SAE from Last Dose (Days)	Cause of Death  Study Day of Death/ Time to Death Since Last Dose (Days)  Adjudication Committee Category
<a href="#">Patient # 29</a> 54/M Lung carcinoma (stage IIIB), pneumothorax, deep upper limb vein thrombosis, brain metastases, bilateral pneumonia, septic shock  62.6 Mild 13/9.9	12 Y Y	VAP  <i>Acinetobacter  baumannii</i>  MIC: 16  (Plasma 56.2%/ ELF 0%)	14 days	Failure/failure  Persistence/ indeterminate	Pneumonia  15/1 Bacteraemia  14/0	Pneumonia, bacteraemia  18/4 2-Yes

Patient Age (Years)/Gender Relevant Medical History Baseline CrCl (mL/min) Renal Impairment [a] APACHE II/MELD	Number of Days from Hospital Admission to Randomization  Prior Antibiotic Tx Within 2 Weeks of Randomization (Y/N)  Prior Antibiotic Tx Failure at Randomization (Y/N)	Infection Dx  Baseline Pathogen  MIC (µg/mL)  (% Time Above MIC Plasma/ELF)	Tx Duration	Clinical Outcome at EOT/TOC  Microbiological Outcome at EOT/TOC	Fatal SAE Preferred Term  SAE Onset Day/ Time to SAE from Last Dose (Days)	Cause of Death  Study Day of Death/ Time to Death Since Last Dose (Days)  Adjudication Committee Category
<b>Patient # 30</b>  71/M  Parkinsonism, pseudomembranous ileus, septic shock, pulmonary oedema  44.8  Moderate  20/14.3	48  Y  Y	HAP  <i>Acinetobacter baumannii</i>  MIC: 0.25  (NA)	3 days	Failure/failure  Indeterminate/ indeterminate	Pneumonia  1/-2	Pneumonia  3/0  2-Yes
<b>Patient # 31</b>  80/F  Upper GI bleeding, urinary tract infection, HAP  17.9  Severe  25/7	23  Y  N	HAP  <i>Acinetobacter baumannii, Klebsiella pneumoniae, Pseudomonas aeruginosa</i>  MIC: 1.0/0.25/0.25  (NA)	12 days	Indeterminate/ failure  Persistence/ indeterminate	Pneumonia  10/-2	Pneumonia aggravated (mechanical ventilation refused by family)  13/1  2-Yes

<b>Patient</b> <b>Age (Years)/Gender</b> <b>Relevant Medical History</b> <b>Baseline CrCl (mL/min)</b> <b>Renal Impairment [a]</b> <b>APACHE II/MELD</b>	<b>Number of Days from Hospital Admission to Randomization</b>  <b>Prior Antibiotic Tx Within 2 Weeks of Randomization (Y/N)</b>  <b>Prior Antibiotic Tx Failure at Randomization (Y/N)</b>	<b>Infection Dx</b>  <b>Baseline Pathogen</b>  <b>MIC (µg/mL)</b>  <b>(% Time Above MIC Plasma/ELF)</b>	<b>Tx Duration</b>	<b>Clinical Outcome at EOT/TOC</b>  <b>Microbiological Outcome at EOT/TOC</b>	<b>Fatal SAE Preferred Term</b>  <b>SAE Onset Day/ Time to SAE from Last Dose (Days)</b>	<b>Cause of Death</b>  <b>Study Day of Death/ Time to Death Since Last Dose (Days)</b>  <b>Adjudication Committee Category</b>
<b>Patient # 32</b>  84/F  Lacunar infarction, pneumonia, infected bed sore, acute kidney injury  13.5  Severe  22/20.7	17  Y  Y	VAP  <i>Stenotrophomonas maltophilia</i>  MIC: 0.06  (Plasma 100%/ ELF 100%)	14 days	Failure/failure  Persistence/ indeterminate	Cardiac arrest  15/1  Septic shock  9/-5	Cardiac arrest  15/1  2-Yes
<b>Patient # 33</b>  73/M  Diabetes mellitus, pneumoconiosis, acute intestinal infarction  31.6  Moderate  18/14.5	26  Y  Y	HAP  <i>Acinetobacter baumannii</i>  MIC: 0.12  (Plasma 100%/ ELF 100%)	14 days	Cure/failure  Eradication/ persistence	Pneumonia  37/23	Pneumonia  37/23  2-No

<b>Patient</b> <b>Age (Years)/Gender</b> <b>Relevant Medical History</b> <b>Baseline CrCl (mL/min)</b> <b>Renal Impairment [a]</b> <b>APACHE II/MELD</b>	<b>Number of Days from Hospital Admission to Randomization</b> <b>Prior Antibiotic Tx Within 2 Weeks of Randomization (Y/N)</b> <b>Prior Antibiotic Tx Failure at Randomization (Y/N)</b>	<b>Infection Dx</b> <b>Baseline Pathogen</b> <b>MIC (µg/mL)</b> <b>(% Time Above MIC Plasma/ELF)</b>	<b>Tx Duration</b>	<b>Clinical Outcome at EOT/TOC</b> <b>Microbiological Outcome at EOT/TOC</b>	<b>Fatal SAE Preferred Term</b> <b>SAE Onset Day/ Time to SAE from Last Dose (Days)</b>	<b>Cause of Death</b> <b>Study Day of Death/ Time to Death Since Last Dose (Days)</b> <b>Adjudication Committee Category</b>
<b>Patient # 34</b> 78/F Myocardial infarction, cholecystitis, ARDS, anoxic brain damage 38.8 Moderate 27/13.8	60 Y Y	cUTI <i>Pseudomonas aeruginosa</i> MIC:1.0 (NA)	2 days	Indeterminate/indeterminate Indeterminate/indeterminate	Septic shock 2/0	Septic shock 2/0 2

APACHE II = Acute Physiology and Chronic Health Evaluation II; AKI = acute kidney injury; ARC = augmented renal clearance; ARDS = acute respiratory distress syndrome; BSI = blood stream infection; COPD = chronic obstructive pulmonary disease; CrCl = creatinine clearance; CT = computed tomography; cUTI = complicated urinary tract infection; Dx = diagnosis; DNR = do not resuscitate; EF = ejection fraction; ELF = epithelial lung fluid; EOT = End of Treatment; F = female; GI = gastrointestinal; HAP = hospital-acquired pneumonia; HCAP = healthcare-associated pneumonia; ID = identification number; M = male; MELD = Model for End-stage Liver Disease; MIC = minimum inhibitory concentration; N = no; NA = not applicable; NYHA = New York Heart Association; PI = principal investigator; SAE = serious adverse event; TOC = Test of Cure; Tx = treatment; UTI = urinary tract infection; VAP = ventilator-associated pneumonia; Y = yes

[a] Baseline CrCl < 30 mL/min = severe; 30 to 50 mL/min = moderate; > 50 to 80 mL/min = mild; > 80 to < 120 mL/min = normal; ≥ 120 mL/min = ARC

**Table 40 List of Patient Profiles of Deaths in the CREDIBLE-CR Study (BAT)**

Patient ID Age (Years)/Gender Relevant Medical History Baseline CrCl (mL/min) Renal Impairment [a] APACHE II/MELD	Number of Days from Hospital Admission to Randomization Prior Antibiotic Tx Within 2 Weeks of Randomization (Y/N) Prior Antibiotic Tx Failure at Randomization (Y/N)	Infection Dx Baseline Pathogen MIC (µg/mL)	BAT Drugs Tx Duration	Clinical Outcome at EOT/TOC Microbiological Outcome at EOT/TOC	Fatal SAE Preferred Term SAE Onset Day/Time to SAE from Last Dose (Days)	Cause of Death Study Day of Death/Time to Death Since Last Dose (Days) Adjudication Committee Category
<b>Adjudication Committee Category 1: death not directly related to the Gram-negative infection for which the patient was randomized</b> 1-A: likely due to the patient's underlying comorbidity 1-B: related to infection other than the original Gram –negative infection 1-C: due to drug-related adverse event 1-D: due to iatrogenic cause 1: cases that did not have a unanimous subcategory vote in Category 1						
Patient # 35 74/M Adenocarcinoma of lung, left upper lobectomy, septic shock, VAP enterobacter cloacae 84.6 Normal 14/8.5	55 Y Y	VAP <i>Acinetobacter baumannii</i> , <i>Enterobacter asburiae</i> MICs: ciprofloxacin: <i>Acinetobacter</i> : > 4 <i>Enterobacter</i> : 1 CFDC: 1 trimethoprim-sulfamethoxazole: <i>Acinetobacter</i> : 1 <i>Enterobacter</i> : 0.5 CFDC: 0.5	Ciprofloxacin, trimethoprim-sulfamethoxazole 9 days	Cure/indeterminate Persistence/indeterminate	Bradycardia 14/5	Bradycardia 14/5 1-A

<b>Patient ID</b> <b>Age (Years)/Gender</b> <b>Relevant Medical History</b> <b>Baseline CrCl (mL/min)</b> <b>Renal Impairment [a]</b> <b>APACHE II/MELD</b>	<b>Number of Days from Hospital Admission to Randomization</b>  <b>Prior Antibiotic Tx Within 2 Weeks of Randomization (Y/N)</b>  <b>Prior Antibiotic Tx Failure at Randomization (Y/N)</b>	<b>Infection Dx</b> <b>Baseline Pathogen</b> <b>MIC (µg/mL)</b>	<b>BAT Drugs</b>  <b>Tx Duration</b>	<b>Clinical Outcome at EOT/TOC</b>  <b>Microbiological Outcome at EOT/TOC</b>	<b>Fatal SAE Preferred Term</b>  <b>SAE Onset Day/ Time to SAE from Last Dose (Days)</b>	<b>Cause of Death</b> <b>Study Day of Death/ Time to Death Since Last Dose (Days)</b>  <b>Adjudication Committee Category</b>
Patient # 36 85/M Benign prostate hyperplasia, bilateral nephrostomy, blood creatinine increased 18.4 Severe 14/20	1 Y N	cUTI <i>Klebsiella pneumoniae</i>  MICs: colistin: 1; fosfomycin: unknown; CFDC: 4	Colistin, fosfomycin 6 days	Indeterminate/indeterminate  Indeterminate/indeterminate	Acute kidney injury, metabolic acidosis, respiratory arrest 6/0 (SAEs assessed related to BAT by PI and sponsor)	Metabolic acidosis due to primary disease  Acute renal failure (per PI) 6/0 1-A
Patient # 37 57/M Liver cirrhosis (CP class C), pseudomembranous colitis 64.8 Mild 14/23.2	20 Y N	HAP <i>Klebsiella pneumoniae</i>  MICs: colistin: ≤ 0.5 cilastatin/ imipenem: 2 CFDC: ≤ 0.03	Colistin, Imipenem-cilastatin 11 days	Indeterminate/indeterminate  Indeterminate/indeterminate	Multiple organ dysfunction syndrome 11/0	Multiple organ failure 11/0 1-B

<b>Patient ID</b> <b>Age (Years)/Gender</b> <b>Relevant Medical History</b> <b>Baseline CrCl (mL/min)</b> <b>Renal Impairment [a]</b> <b>APACHE II/MELD</b>	<b>Number of Days from Hospital Admission to Randomization</b>  <b>Prior Antibiotic Tx Within 2 Weeks of Randomization (Y/N)</b>  <b>Prior Antibiotic Tx Failure at Randomization (Y/N)</b>	<b>Infection Dx</b> <b>Baseline Pathogen</b> <b>MIC (µg/mL)</b>	<b>BAT Drugs</b>  <b>Tx Duration</b>	<b>Clinical Outcome at EOT/TOC</b>  <b>Microbiological Outcome at EOT/TOC</b>	<b>Fatal SAE Preferred Term</b>  <b>SAE Onset Day/Time to SAE from Last Dose (Days)</b>	<b>Cause of Death</b> <b>Study Day of Death/Time to Death Since Last Dose (Days)</b>  <b>Adjudication Committee Category</b>
Patient # 38 77/M Hemorrhagic shock from hemothorax, pneumonia, respiratory failure, acute renal failure, bacteremia 63.2 Mild 20/7.3	47 Y Y	BSI <i>Acinetobacter baumannii</i>  MICs: colistin: > 8 ampicillin-sulbactam: unknown CFDC: 0.25	Ampicillin-sulbactam, colistin 2 days	Failure/failure Indeterminate/indeterminate	Septic shock, multiple organ dysfunction syndrome 9/7	Multiple organ dysfunction syndrome due to septic shock caused by <i>Pseudomonas aeruginosa</i> BSI 10/8 1-B

Patient ID Age (Years)/Gender Relevant Medical History Baseline CrCl (mL/min) Renal Impairment [a] APACHE II/MELD	Number of Days from Hospital Admission to Randomization  Prior Antibiotic Tx Within 2 Weeks of Randomization (Y/N)  Prior Antibiotic Tx Failure at Randomization (Y/N)	Infection Dx Baseline Pathogen MIC (µg/mL)	BAT Drugs  Tx Duration	Clinical Outcome at EOT/TOC  Microbiological Outcome at EOT/TOC	Fatal SAE Preferred Term  SAE Onset Day/Time to SAE from Last Dose (Days)	Cause of Death Study Day of Death/Time to Death Since Last Dose (Days)  Adjudication Committee Category
<b>Adjudication Committee Category 2: death directly related to the Gram-negative infection for which the patient was randomized</b> 2-Yes: infection-related death represent a failure of antibiotic treatment 2-No: infection-related death does not represent a failure of antibiotic treatment 2: cases that did not have a unanimous subcategory vote in Category 2						
<b>Patient # 39</b> 73/F Altered state of consciousness, acute kidney injury, acute liver failure, septic shock 44.1 Moderate 22/28.1	21 Y Y	BSI <i>Klebsiella pneumoniae</i>  MICs: colistin: ≤ 0.5 fosfomycin: unknown CFDC: 8	Fosfomycin, colistin  10 days	Failure/failure  Indeterminate/persistence	Septic shock  16/6	Refractory septic shock  17/7  2-Yes

<b>Patient ID</b> <b>Age (Years)/Gender</b> <b>Relevant Medical History</b> <b>Baseline CrCl (mL/min)</b> <b>Renal Impairment [a]</b> <b>APACHE II/MELD</b>	<b>Number of Days from Hospital Admission to Randomization</b>  <b>Prior Antibiotic Tx Within 2 Weeks of Randomization (Y/N)</b>  <b>Prior Antibiotic Tx Failure at Randomization (Y/N)</b>	<b>Infection Dx</b> <b>Baseline Pathogen</b> <b>MIC (µg/mL)</b>	<b>BAT Drugs</b>  <b>Tx Duration</b>	<b>Clinical Outcome at EOT/TOC</b>  <b>Microbiological Outcome at EOT/TOC</b>	<b>Fatal SAE Preferred Term</b>  <b>SAE Onset Day/ Time to SAE from Last Dose (Days)</b>	<b>Cause of Death</b> <b>Study Day of Death/ Time to Death Since Last Dose (Days)</b>  <b>Adjudication Committee Category</b>
<b>Patient # 40</b> 84/F Hemodialysis, pneumonia, acute respiratory failure, decubitus ulcers 37.1 Moderate 22/19.7	3 Y N	VAP <i>Klebsiella pneumoniae</i>  MICs: colistin: ≤ 0.5; tigecycline: 1; CFDC:4	Colistin, tigecycline 12 days	Failure/failure Persistence/persistence	Cardiac arrest 24/12	Septicemia with chronic renal failure, cardiopulmonary arrest that developed during sepsis 24/12 2-Yes
<b>Patient # 41</b> 69/M Colon cancer, colectomy and ileostomy, fecal peritonitis, subphrenic abscess, septic shock, renal failure 128.6 ARC 18/24.3	67 Y N	BSI <i>Pseudomonas aeruginosa</i>  MICs: ceftazidime, ciprofloxacin: 0.5 CFDC: 0.5	Ceftazidime, ciprofloxacin 15 days	Failure/failure Indeterminate/indeterminate	General physical health deterioration 24/9	General physical health deterioration 24/9 2-Yes

<b>Patient ID</b> <b>Age (Years)/Gender</b> <b>Relevant Medical History</b> <b>Baseline CrCl (mL/min)</b> <b>Renal Impairment [a]</b> <b>APACHE II/MELD</b>	<b>Number of Days from Hospital Admission to Randomization</b>  <b>Prior Antibiotic Tx Within 2 Weeks of Randomization (Y/N)</b>  <b>Prior Antibiotic Tx Failure at Randomization (Y/N)</b>	<b>Infection Dx</b> <b>Baseline Pathogen</b> <b>MIC (µg/mL)</b>	<b>BAT Drugs</b>  <b>Tx Duration</b>	<b>Clinical Outcome at EOT/TOC</b>  <b>Microbiological Outcome at EOT/TOC</b>	<b>Fatal SAE Preferred Term</b>  <b>SAE Onset Day/Time to SAE from Last Dose (Days)</b>	<b>Cause of Death</b> <b>Study Day of Death/Time to Death Since Last Dose (Days)</b>  <b>Adjudication Committee Category</b>
<b>Patient # 42</b> 42/M End stage renal disease, pancreatoduodenectomy, cardiac arrest 15.9 Severe 14/25.6	65 Y Y	VAP <i>Acinetobacter baumannii</i>  MICs: colistin: 2 cefipime: > 16 CFDC: 0.5	Colistin, cefipime 12 days	Failure/ indeterminate  Persistence/ indeterminate	Acute respiratory failure, cardiac arrest 13/1	Acute respiratory failure, cardiac arrest (DNR) 13/1 2-Yes
<b>Patient # 43</b> 62/M Liver cirrhosis, ureterolithiasis, hydronephrosis, septic shock 270.8 ARC 13/8.4	8 Y Y	cUTI <i>Pseudomonas aeruginosa</i>  MICs: colistin: 1 CFDC: 2	Colistin 6 days	Failure/failure Indeterminate/ indeterminate	Device related infection 2/-4  Septic shock 6/0	Septic shock aggravated, central vein catheter-related bloodstream infection 6/0 2-No

<b>Patient ID</b> <b>Age (Years)/Gender</b> <b>Relevant Medical History</b> <b>Baseline CrCl (mL/min)</b> <b>Renal Impairment [a]</b> <b>APACHE II/MELD</b>	<b>Number of Days from Hospital Admission to Randomization</b> <b>Prior Antibiotic Tx Within 2 Weeks of Randomization (Y/N)</b> <b>Prior Antibiotic Tx Failure at Randomization (Y/N)</b>	<b>Infection Dx</b> <b>Baseline Pathogen</b> <b>MIC (µg/mL)</b>	<b>BAT Drugs</b> <b>Tx Duration</b>	<b>Clinical Outcome at EOT/TOC</b> <b>Microbiological Outcome at EOT/TOC</b>	<b>Fatal SAE Preferred Term</b> <b>SAE Onset Day/Time to SAE from Last Dose (Days)</b>	<b>Cause of Death</b> <b>Study Day of Death/Time to Death Since Last Dose (Days)</b> <b>Adjudication Committee Category</b>
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APACHE = Acute Physiology and Chronic Health Evaluation II; ARC = augmented renal clearance; BAT = best available therapy; BSI = blood stream infection; CFDC = cefiderocol; CP = Child–Pugh; CRBSI = catheter-related bloodstream infection; CrCl = creatinine clearance; cUTI = complicated urinary tract infection; DNR = do not resuscitate; Dx = diagnosis; EOT = End of Treatment; F = female; HAP = hospital-acquired pneumonia; ID = identification number; M = male; MELD = Model for End-stage Liver Disease; MIC = minimum inhibitory concentration; N = no; PI = principal investigator; SAE = serious adverse event; TOC = Test of Cure; Tx = treatment; VAP = ventilator-associated pneumonia; Y = yes

[a] Baseline CrCl < 30 mL/min = severe; 30 to 50 mL/min = moderate; > 50 to 80 mL/min = mild; > 80 to < 120 mL/min = normal; ≥ 120 mL/min = ARC

### 10.7.3 Mortality Summary

The overall protocol-defined clinical and microbiological outcome data do not suggest a lack of cefiderocol efficacy as causative for the all-cause mortality difference with similar results for both treatment groups.

There was also no pattern in cause of death that Shionogi could find in the CREDIBLE-CR study that pointed to a toxic mechanism attributable to cefiderocol.

Patient Profiles of the 43 deaths is provided in [Table 39](#) (cefiderocol treated patients) and [Table 40](#) (BAT treated patients). Of these deaths, only one was considered by the treating investigator to be related to treatment (ie, an adverse drug reaction) and this was for the BAT death (patient (b) (6)) as listed in Table 40.

Detailed narratives for patients whose death was adjudicated as due to the baseline Gram-negative infection for which they were randomized into the study are provided in [Appendix 15.7](#) to give clinical context to this outcome.

## 10.8 CREDIBLE-CR Summary

The CREDIBLE-CR study assessed cefiderocol, and an individualized Best Available Therapy (BAT) regimen in seriously ill patients with carbapenem-resistant Gram-negative infections. Efficacy assessments, which were the primary objectives of the study, suggested that both cefiderocol and BAT have comparable efficacy with regard to pre-specified clinical and microbiological outcomes. Adverse events and serious adverse events were generally similar between treatment arms.

Shionogi acknowledges the serious nature of the outcome of all-cause mortality. We have examined in detail each of the individual fatal cases, and more than 30 baseline factors, examined the adverse events and other measures of toxicity, examined the results for lack of efficacy and provided the data to a blinded panel of experts. Based on the aggregate results, we have found possible hypotheses, but found no conclusive reasons for the mortality difference seen in CREDIBLE-CR. Shionogi is of the opinion that the difference in mortality is best understood by examining the detailed patient level information which gives a clear picture of the clinical context that led to the outcome of death.

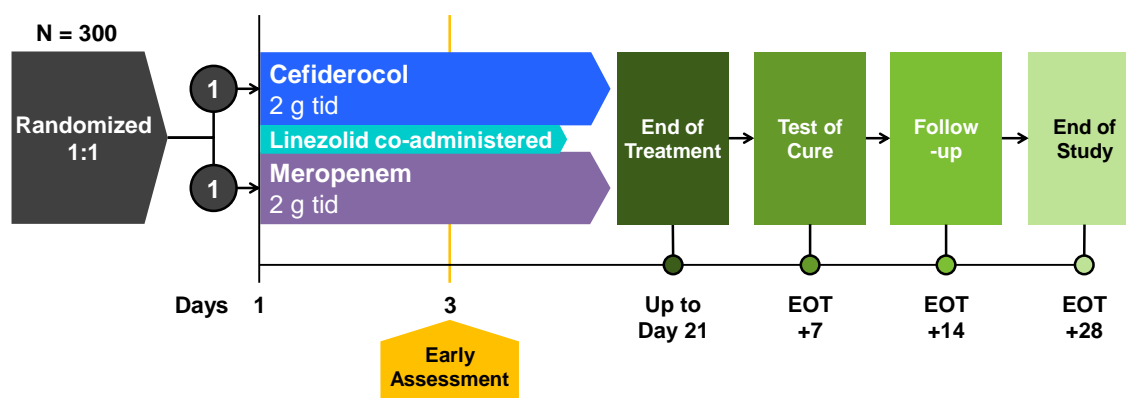
## 11 APEKS-NP STUDY

### 11.1 Study Design

The APEKS-NP study is pivotal for a potential future indication of nosocomial pneumonia, and information included here is not in the current NDA; the study is briefly discussed because it provides newly available information relevant to the safety and mortality discussion.

APEKS-NP was a Phase 3 global, double-blind, randomized, active-controlled, non-inferiority study in 300 adult patients with documented nosocomial pneumonia caused by Gram-negative bacteria (Figure 25). Overall, 148 patients were randomized to the cefiderocol arm and 152 to the meropenem arm, although 2 patients in the meropenem arm did not receive study drug. Patients meeting eligibility criteria were randomized (1:1) to 7 to 14 days of IV treatment with either cefiderocol 2 g or meropenem 2 g, both administered q8h over 3 hours. Linezolid was additionally administered for at least 5 days in both arms to provide coverage for methicillin-resistant *Staphylococcus aureus* (MRSA) and, in the cefiderocol group, for Gram-positive bacteria.

**Figure 25 APEKS-NP Study Design**



EOT, end of treatment; tid, three times daily.

The primary endpoint was all-cause mortality at Day 14 for the mITT population, defined as all treated patients except those that had Gram-positive pathogens only identified at baseline. The non-inferiority margin was predefined as 12.5%. Secondary endpoints included clinical and microbiological outcomes assessed at Early Assessment (EA), End of Treatment (EOT), Test of Cure (TOC), and Follow-up (FU), as well as Day 28 all-cause mortality.

### 11.2 Study Results

The study met the primary endpoint of demonstrating cefiderocol non-inferiority to meropenem at Day 14. [Table 41](#) shows mortality data at Day 14 in the mITT population. [Table 42](#) shows the mortality data for Day 14, Day 28, and overall mortality in the ITT population ([Wunderink 2019](#)).

**Table 41 Day 14 All-Cause Mortality in the APEKS-NP Study (mITT Population)**

Time point	Cefiderocol N=145 n/N' (%)	Meropenem N = 147 n/N' (%)	Treatment Comparison Difference (%) 95% CI
Day 14	18/145 (12.4)	17/146 (11.6)	0.8 (-6.6, 8.2)

**Table 42 All-Cause Mortality in the APEKS-NP Study (ITT Population)**

Time point	Cefiderocol N=148 n/N' (%)	Meropenem N = 150 n/N' (%)	Treatment Comparison Difference (%) 95% CI
Day 14	19/148 (12.8)	17/149 (11.4)	1.4 (-6.0, 8.7)
Day 28	31/146 (21.2)	30/149 (20.1)	1.1 (-8.0, 10.3)
End of study	39/145 (26.9)	34*/149 (22.8)	4.1 (-5.6, 13.8)

CI, confidence interval, N'= number of patients with known survival status. \* (b) (6) in the meropenem group died 1 day after EOS, due to SAE occurred during the study, is not captured here.

### Comparison between CREDIBLE-CR and APEKS-NP Study Populations

The magnitude of the mortality difference observed in the CREDIBLE-CR study was not observed in the APEKS-NP study. The patient population from the APEKS-NP study is compared to the cohort of HAP/VAP/HCAP patients in the CREDIBLE-CR study, including ventilated status, severity of illness, age, renal function, and baseline pathogens in [Table 43](#). Comparison to the CREDIBLE-CR patients with nosocomial pneumonia (N=67) shows some differences between CREDIBLE-CR nosocomial pneumonia subgroup and APEKS-NP in the predominant infecting pathogens (*Acinetobacter baumannii* 55.2% vs 16%, respectively) and the proportion of patients who were treatment failures prior to randomization (64% vs 32.5%, respectively).

**Table 43**                      **Comparison of the Demographic, Clinical, and Microbiological Parameters Between the CREDIBLE-CR and APEKS-NP Study Populations (ITT Populations)**

<b>Variable</b>	<b>CREDIBLE-CR N = 150</b>	<b>CREDIBLE-CR, HAP/VAP/HCAP n = 67</b>	<b>APEKS-NP N = 298</b>
HAP, %	18.0	40.3	40.6
VAP, %	24.7	55.2	41.9
HCAP, %	2.0	4.5	17.4
Ventilated, %	51.0	74.6	59.7
Mean age, y	63.1	63.9	65.2
Male gender, %	67.3	76.1	68.8
Region, %			
Europe	56.7	40.3	66.8
Asia-Pacific	28.7	38.8	29.2
North and South America	14.7	20.8	4.0
CrCL < 50 mL/min, %	38.7	32.8	33.9
APACHE II score ≥ 16, %	45.3	56.7	48.7
Mean score	15.3	17.1	16.2
Treatment failure, %	47.3	64.2	32.6
Top 4 Baseline pathogen, %			
<i>A. baumannii</i>	37.3	55.2	15.8
<i>K. pneumoniae</i>	33.3	25.4	30.9
<i>P. aeruginosa</i>	19.3	25.4	16.1
<i>E. coli</i>	6.0	7.5	13.8

APACHE II, Acute Physiology and Chronic Health Evaluation II; CrCl, creatinine clearance; HAP; hospital-acquired pneumonia; HCAP; healthcare-associated pneumonia; VAP, ventilator-associated pneumonia.

## 12 COMPASSIONATE USE

Cefiderocol has been provided upon unsolicited request from attending physicians to patients with serious CR Gram-negative infections who have no other treatment options. More than 200 requests for compassionate use have been received from around the world. The criteria for fulfilling these requests are highly restrictive. All other available treatments must be ruled out through susceptibility testing and/or evidence of treatment failure in efficacy or safety, and patients must be unable to enroll in clinical studies of cefiderocol.

Of those who met these criteria, Shionogi confirmed that 74 patients completed cefiderocol therapy in compassionate use. The FDA has supported Shionogi in fulfilling requests in the US. A tabular listing of patient information is available in [Appendix 15.8](#). Two cases have been published, one involving successful treatment of native aortic valve endocarditis caused by *P. aeruginosa* infection ([Edgeworth 2018](#)) and another patient with bacteremia pneumonia caused by XDR *Acinetobacter baumannii* and KPC producing *Klebsiella pneumoniae* ([Trecarichi 2019](#)). Additionally, two cases of *Achromobacter xylosoxidans* in patients with cystic fibrosis awaiting lung transplantation will be described at Infectious Disease Week 2019 ([Warner 2019](#)).

By the time compassionate use was requested, these patients were severely ill or were at risk of disease progression as there was no alternative therapy due to antibiotic resistance or to limitations of therapy, eg, acute kidney injury due to colistin or poor serum concentrations of tigecycline for BSIs. Infection sites were varied and included bloodstream, respiratory, urinary and gastrointestinal tracts, bone, and prosthetic devices. Multiple risk factors were reported in most patients. They included conditions which were excluded from the clinical studies such as endocarditis, osteomyelitis, and cystic fibrosis. Of the 74 patients treated, 49 patients survived, 17 died due to their underlying infection, 6 died for reasons other than the original bacterial infection, and the remainder had unknown outcomes. Of the 49 that survived, 3 of these patients subsequently died due to other causes. Over 60 % of the patients receiving cefiderocol survived when no other viable treatment option was available to them. Of those patients who died due to their infection, 6 received cefiderocol for less than 4 days. Of those 6 patients, 2 patients received cefiderocol for less than 2 days. Fourteen patients received cefiderocol for more than 10 days. Non-fermenter species accounted for almost all isolates, with the most common being *P. aeruginosa* (n = 30); *A. baumannii* complex (n = 24), *Achromobacter xylosoxidans* (n = 10), *Burkholderia cepacia* complex (n = 9), Enterobacterales (n = 9), and *S. maltophilia* (n = 3). Eight patients had mixed infections with various MDR organisms. All isolates were multidrug resistant with some being pan-resistant to currently available classes of antimicrobial agents. Two strains had MICs > 4 µg/mL to cefiderocol.

The longest use of cefiderocol was for more than 90 days in a renal transplant patient who had a *P. aeruginosa* infection of the intervertebral disc with no apparent safety issues. All cases were managed by the physician requesting compassionate use and the outcome was reported to Shionogi. Serious AEs were reported following the regulatory requirements. They provide real world evidence of the ongoing clinical need.

## 13 BENEFIT-RISK ASSESSMENT

There is an urgent unmet medical need for effective and safe new treatments for cUTI caused by MDR, particularly CR Gram-negative bacteria. Carbapenem-resistant infections are typically healthcare associated, meaning that the patients are already hospitalized or under care for often significant conditions. The growing numbers of elderly, surgical, and immunocompromised patients comprise an increasing population at risk for these infections. Patients with cUTI caused by CR pathogens have longer hospital and ICU stays and increased mortality, compared with those infected by carbapenem-susceptible strains (Premier Research database, [Zilberberg 2017](#)).

The increase in CR Gram-negative infections, of which cUTI make up a substantial proportion, is a serious national and global public health challenge. However, at present, there are few safe and effective treatment options for patients with these severe infections. The multiple resistance mechanisms of the pathogens and the toxicities of some available medications, such as colistin/polymyxin, require a new approach to treatment in order to save lives.

Cefiderocol is currently the only antibiotic that potentially meets this need. Cefiderocol addresses all 3 mechanisms of carbapenem resistance in Gram-negative pathogens. Its novel mechanism of cell entry that overcomes porin channel and efflux pump mutations and its stability against all carbapenemases make cefiderocol an important new contribution to the battle against highly resistant Gram-negative infection. The safety profile of cefiderocol is consistent with that of a typical cephalosporin.

Cefiderocol is proposed for the treatment of cUTI, with an indication restricted to use in patients with limited or no treatment alternatives. It will therefore be used primarily in older hospitalized patients with serious comorbidities and highly resistant infections – patients with a defined and immediate risk for whom inappropriate initial treatment present a decided danger.

In the nonclinical development program, an extensive series of in vitro studies, clinical specimens from extensive surveillance studies, and animal infection models demonstrated the efficacy of cefiderocol against Enterobacteriaceae, *P. aeruginosa*, *A. baumannii*, *S. maltophilia*, *Enterobacter cloacae*, *Serratia marcescens*, and *B. cepacia*, including CR strains. Studies have shown cefiderocol to be stable against all known classes of  $\beta$ -lactamases, including carbapenemases. These findings confirm the ability of cefiderocol to overcome multiple mechanisms of resistance, including porin and efflux pump mutations, unlike other  $\beta$ -lactam or  $\beta$ -lactam/ $\beta$ -lactamase antibiotics.

The cUTI study demonstrated that in a hospitalized population of 448 patients, with multiple comorbidities and difficult-to-treat infections, cefiderocol was noninferior to a standard-of-care antibiotic comparator, high dose IPM/CS. Although the study was only designed to demonstrate noninferiority, the findings of a post-hoc analysis were consistent with superiority. The adjusted treatment difference favored cefiderocol by 18 % and the lower limit of the 95 % confidence interval exceeded 0.

The patient population in the cUTI study was elderly, with a median age of 66 years and 24 % > 75 years of age. The demonstration of efficacy and safety in an elderly population, with no difference from the results seen in younger patients, further supports the benefit of cefiderocol. Consistent efficacy and safety were also confirmed in patients with varying degrees of renal function.

In the cUTI study, the clinical and microbiological activity of cefiderocol was demonstrated for infections caused by *E. coli*, *K. pneumoniae*, *P. aeruginosa*, *Proteus mirabilis*, *Klebsiella oxytoca*, *E. cloacae* with *E. cloacae* complex, *Enterobacter aerogenes*, *Citrobacter freundii* with *C. freundii* complex, *Morganella morganii*, and *S. marcescens*. The benefit of cefiderocol was further illustrated by comprehensive sensitivity and subgroup analyses, including in ESBL-producing organisms.

The safety of cefiderocol was established through extensive toxicology studies and nonclinical and clinical pharmacology programs, including a thorough QT/QTc study, and in the pivotal cUTI study. The findings from 300 patients treated with cefiderocol in the cUTI study provide the clinical safety database appropriate for a limited-use indication in patients with severe and life-threatening infections where existing therapies are either ineffective or potentially toxic.

In the cUTI study, the comparator IPM/CS was an established standard of care  $\beta$ -lactam antibiotic with a well-defined safety profile. The patient population was appropriate for the safety evaluation of cefiderocol, consisting of hospitalized, mainly elderly individuals with significant comorbidities, concomitant medications, and severe infections requiring 7 to 14 days of IV therapy.

The most common AEs associated with cefiderocol in the cUTI study occurring at rates of > 5 % included diarrhea, hypertension, and constipation. The rates of these AEs and of AEs in general were similar to or lower than those of the IPM/CS comparator. Serious AEs occurred at a lower rate with cefiderocol than with IPM/CS and were generally unrelated to treatment. One patient treated with cefiderocol died during the study; the death was not considered to be related to treatment.

Patients with moderate and severe renal impairment were included in the cUTI study. No safety concern in these patients was identified. Dose adjustments for varying degrees of renal function, including patients with augmented renal clearance, will be recommended to ensure equivalent drug exposure. No serious rash or hypersensitivity was reported, and no liver abnormality reaching Hy's law criteria or drug-induced liver injury was observed. No excess of AEs related to iron homeostasis parameters was observed in cefiderocol-treated patients compared with those receiving the comparator.

$\beta$ -lactam antibiotics have been associated with seizures, generally where exposures have been high. Although 1 patient with a history of epilepsy was reported to have had a seizure in the cUTI study, dosing with cefiderocol was continued uneventfully. There was no evidence of de novo seizure associated with cefiderocol. The safety margin established from nonclinical studies for the development of seizures is 17 times the human exposure at 2 g of cefiderocol dosed q8h over 8 hours.

Cefiderocol has little to no potential for DDIs, and co-administration of other drugs is not expected to affect the PK of cefiderocol (or of the other drugs). No dose adjustment is required for hepatic impairment.

Overall in the cUTI study, there was no new safety signal beyond what is already known about the cephalosporin class. Cefiderocol was well tolerated, with few serious events and a low rate of *C. difficile*-related diarrhea.

The CREDIBLE-CR study of carbapenem-resistant infection was designed to collect real-world clinical information from patients with significant comorbidities and poor prognoses regardless of the site of infection being treated. The study showed that clinical outcome, microbiological outcome, and the AE profile of the 2 treatment arms were comparable. An all-cause mortality difference was observed and each death has been carefully assessed by the investigator, Shionogi, and independent analysts, with no evidence of an adverse drug reaction or attributable AE due to cefiderocol treatment. The magnitude of this difference in all-cause mortality was not observed in the larger, double blind APEKS-NP study where the study was designed to test all-cause mortality.

Shionogi acknowledges the serious nature of this outcome. We have examined in detail each of the individual fatal cases, and more than 30 baseline factors, examined the adverse events and other measures of toxicity, examined the results for lack of efficacy, provided the data to a blinded panel of experts, compared the results in CREDIBLE-CR to both the cUTI and APEKS-NP studies, and based on the aggregate results for all-cause mortality, have found possible hypotheses, but no conclusive alternate reasons for the mortality difference seen in CREDIBLE-CR. Shionogi is of the opinion that the difference in mortality is best understood by examining the detailed patient level information in the study which give a clear picture of the clinical context that led to the outcome of death or attributable mortality.

The proposed indication for cefiderocol is for limited use in cUTI, where limited or no alternative treatment options are available. These are patients with serious conditions requiring hospitalization and for whom rapid effective treatment is critical as their cUTI is often superimposed on multiple comorbidities. For these patients, the urgent medical need and the demonstrable benefits of cefiderocol outweigh the observed and/or predictable risks.

Appropriate antibiotic stewardship and clinical supervision will ensure that the efficacy and safety benefits of cefiderocol will be fully realized and preserved.

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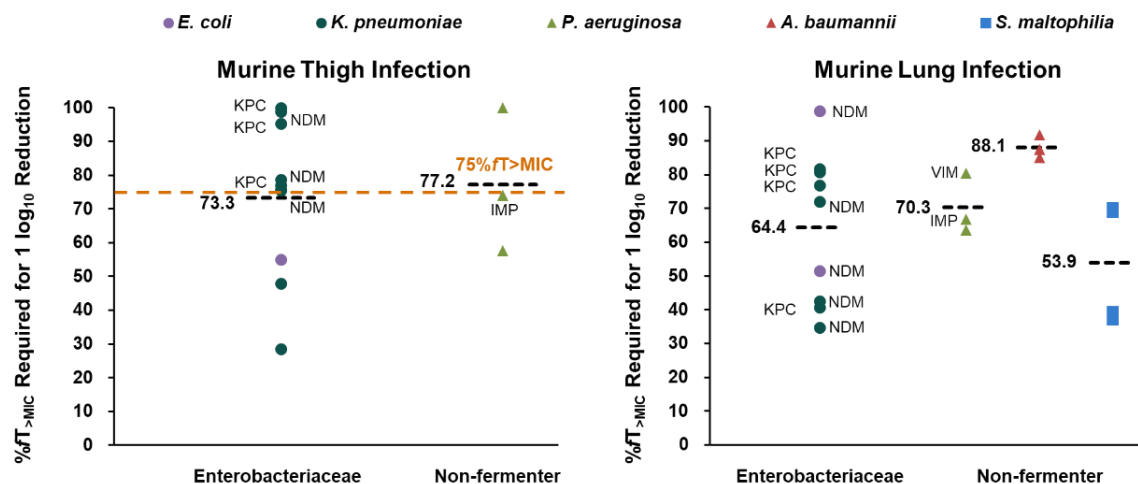
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## **15 APPENDICES**

## 15.1 Appendix 1 – Summary Results of PK/PD in Thigh/Lung Infection Models

### The $fT_{>MIC}$ Required for 1 Log Reduction in the Dose Ranging Study Using Mouse Thigh/Lung Infection Models



### The $fT_{>MIC}$ Required for Static Effect, 1 Log Reduction and 2 Log Reduction in the Dose Ranging Study Using Mouse Thigh Infection Models

Test organism	MIC (µg/mL)	% $fT_{>MIC}$		
		Static effect	1-log <sub>10</sub> reduction	2-log <sub>10</sub> reduction*
<i>E. coli</i> ATCC 25922	0.125	40	55	70
<i>K. pneumoniae</i> ATCC 13883	0.25	35.4	47.9	65
<i>K. pneumoniae</i> 1478266	0.5	11.3	28.5	Not achieved (max 1.8 log reduction)
<i>K. pneumoniae</i> 1478677	0.25	55.1	78.8	Not achieved (max 1.90 log reduction)
<i>K. pneumoniae</i> VA-357	2	68.4	77	100
<i>K. pneumoniae</i> VA-384	4	93.6	100	Not achieved (max: 1 log reduction)
<i>K. pneumoniae</i> VA-391	4	87.3	95.3	Not achieved (max 1.8 log reduction)
<i>K. pneumoniae</i> 6560-MAR	2	96.3	98.9	Not achieved (max 1.3 log reduction)
<i>K. pneumoniae</i> KI2	8	68.9	75.6	90
<i>K. pneumoniae</i> NCTC 13443	16	68.7	75.8	85
<i>P. aeruginosa</i> ATCC 27853	0.5	78.5	100	Not achieved (max 1 log reduction)
<i>P. aeruginosa</i> SR27001	2	63.1	74.1	90

## The $fT_{>MIC}$ Required for Static Effect, 1 Log Reduction and 2 Log Reduction in the Dose Ranging Study Using Mouse Lung Infection Models

Test organism	MIC ( $\mu\text{g/mL}$ )	% $fT_{>MIC}$		
		Static effect	1- $\log_{10}$ reduction	2- $\log_{10}$ reduction
<i>E. coli</i> AB	4	98	98.9	100
<i>E. coli</i> IR-5	4	34.9	51.5	80
<i>K. pneumoniae</i> VA-357	2	32.5	40.8	55
<i>K. pneumoniae</i> VA-361	4	72.6	81.8	90
<i>K. pneumoniae</i> VA-384	4	65.0	76.9	90
<i>K. pneumoniae</i> VA-391	4	68.2	80.8	Not achieved (max 1.7 log reduction)
<i>K. pneumoniae</i> 6560-MAR	2	60.6	72	90
<i>K. pneumoniae</i> KI2	8	34.2	42.6	55
<i>K. pneumoniae</i> NCTC 13443	16	26.1	34.7	60
<i>P. aeruginosa</i> ATCC 27853	0.5	53.7	66.8	80
<i>P. aeruginosa</i> SR27001	2	49.6	63.6	85
<i>P. aeruginosa</i> NCTC 13437	1	69.0	80.5	95
<i>A. baumannii</i> BEN ST BRI	0.25	87.1	91.8	95
<i>A. baumannii</i> 1485247	2	78.2	85	95
<i>A. baumannii</i> NCTC 13301	1	80.8	87.5	95
<i>S. maltophilia</i> 1146824	0.125	61.0	69.0	80
<i>S. maltophilia</i> 1371071	0.125	62.9	70.1	80
<i>S. maltophilia</i> 1392567	0.25	29.9	37.2	45
<i>S. maltophilia</i> 1444463	0.25	28.6	39.4	50

## 15.2 Appendix 2 – Probability of Target Attainment in Plasma and ELF for 75%, 90%, and 100% fT>MIC by Infection Site and Renal Function

### (a) PTA in plasma and ELF for 75% fT>MIC

Infection	Renal function group	Dose regimens with 3-hr infusion	MIC (µg/mL)					
			0.25	0.5	1	2	4	8
HAP/VAP/HCAP	Plasma	Augmented renal function	100	100	100	99.9	99.8	97.7
		Normal renal function	100	100	100	99.9	99.7	96.3
		Mild renal impairment	100	100	100	100	100	99.0
		Moderate renal impairment	100	100	100	100	100	99.8
		Severe renal impairment	100	100	100	100	100	99.7
		ESRD	100	100	100	100	100	99.8
	ELF	Augmented renal function	100	100	99.8	97.3	72.6	19.0
		Normal renal function	100	99.9	99.7	95.8	68.8	13.1
		Mild renal impairment	100	100	100	98.9	87.2	33.4
		Moderate renal impairment	100	100	100	99.8	92.7	42.9
		Severe renal impairment	100	100	100	100	96.5	56.7
		ESRD	100	100	100	100	92.9	44.2
BSI/sepsis	Plasma	Augmented renal function	100	100	99.9	99.8	99.3	92.9
		Normal renal function	100	100	100	99.9	98.6	90.7
		Mild renal impairment	100	100	100	100	99.6	97.1
		Moderate renal impairment	100	100	100	100	100	99.2
		Severe renal impairment	100	100	100	100	100	99.4
		ESRD	100	100	100	100	99.9	99.6
cUTI/AUP	Plasma	Augmented renal function	100	100	99.9	99.8	98.9	89.7
		Normal renal function	100	100	100	99.7	97.4	88.9
		Mild renal impairment	100	100	100	100	99.4	95.6
		Moderate renal impairment	100	100	100	100	100	98.9
		Severe renal impairment	100	100	100	100	100	99.2
		ESRD	100	100	100	100	99.9	99.3

PK steady state was assumed. PTA is shown in percent (%).

Augmented: CrCL ≥ 120 mL/min (120 to < 150 = 50%; 150 to < 200 = 30%; ≥ 200 = 20%) Normal: CrCL 90 to < 120 mL/min

Mild: CrCL 60 to < 90 mL/min Moderate: CrCL 30 to < 60 mL/min Severe: CrCL 15 to < 30 mL/min ESRD: CrCL 5 to < 15 mL/min

1000 simulated patients in each simulation scenario

Body weight was assumed to be log-normal distributed with geometric mean of 72.4 kg and CV of 30%

**(b) PTA in plasma and ELF for 90%  $fT_{>MIC}$**

Infection	Renal function group	Dose regimens with 3-hr infusion	MIC (µg/mL)						
			0.25	0.5	1	2	4	8	16
HAP/VAP/HCAP	Plasma	Augmented renal function	100	100	99.8	99.8	98.7	90.8	61.2
		Normal renal function	100	100	100	99.7	97.8	91.0	56.1
		Mild renal impairment	100	100	100	100	99.4	96.3	79.7
		Moderate renal impairment	100	100	100	100	100	99.2	88.1
		Severe renal impairment	100	100	100	100	100	99.6	94.8
		ESRD	100	100	100	100	99.9	99.7	91.1
	ELF	Augmented renal function	100	100	98.6	89.5	58.5	13.5	0.3
		Normal renal function	100	99.7	97.6	89.5	52.0	8.6	0.0
		Mild renal impairment	100	100	99.4	96.0	77.9	25.1	1.2
		Moderate renal impairment	100	100	100	99.0	87.1	36.1	1.9
		Severe renal impairment	100	100	100	99.4	94.0	51.0	4.2
		ESRD	100	100	100	100	90.2	38.7	3.9
BSI/sepsis	Plasma	Augmented renal function	100	99.8	99.8	99.1	96.5	82.1	41.7
		Normal renal function	100	100	99.7	98.8	95.2	79.4	36.0
		Mild renal impairment	100	100	100	99.6	98.6	91.4	60.9
		Moderate renal impairment	100	100	100	100	99.7	97.3	76.5
		Severe renal impairment	100	100	100	100	99.8	98.8	87.7
		ESRD	100	100	100	100	99.9	98.4	81.3
cUTI/AUP	Plasma	Augmented renal function	100	99.8	99.8	98.7	95.0	76.8	37.7
		Normal renal function	100	100	99.6	97.9	93.4	74.0	32.0
		Mild renal impairment	100	100	100	99.5	97.7	88.7	56.5
		Moderate renal impairment	100	100	100	100	99.7	96.2	71.3
		Severe renal impairment	100	100	100	100	99.7	98.6	85.3
		ESRD	100	100	100	100	99.8	97.8	79.7

PK steady state was assumed. PTA is shown in percent (%).

Augmented: CrCL ≥ 120 mL/min (120 to < 150 = 50%; 150 to < 200 = 30%; ≥ 200 = 20%) Normal: CrCL 90 to < 120 mL/min

Mild: CrCL 60 to < 90 mL/min Moderate: CrCL 30 to < 60 mL/min Severe: CrCL 15 to < 30 mL/min ESRD: CrCL 5 to < 15 mL/min

1000 simulated patients in each simulation scenario

Body weight was assumed to be log-normal distributed with geometric mean of 72.4 kg and CV of 30%

**(c) PTA in plasma and ELF for 100%  $fT_{>MIC}$**

Infection	Renal function group	Dose regimens with 3-hr infusion	MIC (µg/mL)						
			0.25	0.5	1	2	4	8	16
HAP/VAP/HCAP	Plasma	Augmented renal function	100	99.9	99.8	99.7	98.1	88.0	57.6
		Normal renal function	100	100	99.9	99.2	96.8	87.3	49.2
		Mild renal impairment	100	100	100	100	99.2	94.8	74.9
		Moderate renal impairment	100	100	100	100	99.9	98.8	85.9
		Severe renal impairment	100	100	100	100	100	99.4	93.5
		ESRD	100	100	100	100	99.9	99.6	89.9
	ELF	Augmented renal function	100	100	98.0	87.1	54.7	12.1	0.3
		Normal renal function	100	99.1	96.5	85.9	47.2	7.1	0.0
		Mild renal impairment	100	100	99.2	94.1	72.1	21.6	1.0
		Moderate renal impairment	100	100	100	98.3	84.3	32.9	1.8
		Severe renal impairment	100	100	100	99.3	92.7	48.5	3.8
		ESRD	100	100	100	99.4	89.1	36.8	3.8
BSI/sepsis	Plasma	Augmented renal function	99.9	99.8	99.8	98.8	95.1	78.2	38.5
		Normal renal function	100	100	99.6	97.8	93.2	73.8	31.6
		Mild renal impairment	100	100	100	99.4	97.6	88.6	56.1
		Moderate renal impairment	100	100	100	100	99.7	96.0	71.0
		Severe renal impairment	100	100	100	100	99.6	98.5	85.1
		ESRD	100	100	100	100	99.8	97.8	79.4
cUTI/AUP	Plasma	Augmented renal function	99.9	99.8	99.6	98.3	92.8	73.0	34.3
		Normal renal function	100	99.8	99.0	97.1	90.9	67.4	27.8
		Mild renal impairment	100	100	100	99.2	95.8	85.7	50.3
		Moderate renal impairment	100	100	100	99.9	99.0	93.5	67.2
		Severe renal impairment	100	100	100	100	99.6	98.1	82.3
		ESRD	100	100	100	99.9	99.8	96.8	77.5

PK steady state was assumed. PTA is shown in percent (%).

Augmented: CrCL ≥ 120 mL/min (120 to < 150 = 50%; 150 to < 200 = 30%; ≥ 200 = 20%) Normal: CrCL 90 to < 120 mL/min

Mild: CrCL 60 to < 90 mL/min Moderate: CrCL 30 to < 60 mL/min Severe: CrCL 15 to < 30 mL/min ESRD: CrCL 5 to < 15 mL/min

1000 simulated patients in each simulation scenario

Body weight was assumed to be log-normal distributed with geometric mean of 72.4 kg and CV of 30%

### 15.3 Appendix 3 – CREDIBLE-CR Study: Study Subject Full Demographics and Baseline Characteristics Listing

	Cefiderocol (N = 101)	BAT (N = 49)	Total (N = 150)
Age (years)			
N	101	49	150
Mean	63.1	63.0	63.1
Standard deviation	19.0	16.7	18.2
Median	69.0	62.0	68.5
Minimum	19	19	19
Maximum	92	92	92
Age group (n, %)			
< 65 years	37 (36.6)	27 (55.1)	64 (42.7)
≥ 65 years	64 (63.4)	22 (44.9)	86 (57.3)
Gender (n, %)			
Male	66 (65.3)	35 (71.4)	101 (67.3)
Female	35 (34.7)	14 (28.6)	49 (32.7)
Race (n, %)			
White	63 (62.4)	32 (65.3)	95 (63.3)
Asian	29 (28.7)	14 (28.6)	43 (28.7)
Other	9 (8.9)	3 (6.1)	12 (8.0)
Ethnicity (n, %)			
Hispanic or Latino	13 (12.9)	3 (6.1)	16 (10.7)
Not Hispanic or Latino	82 (81.2)	44 (89.8)	126 (84.0)
Not reported	6 (5.9)	2 (4.1)	8 (5.3)
Region (n, %)			
North America	6 (5.9)	3 (6.1)	9 (6.0)
South America	9 (8.9)	4 (8.2)	13 (8.7)
Europe	57 (56.4)	28 (57.1)	85 (56.7)
Asia-Pacific	29 (28.7)	14 (28.6)	43 (28.7)
Total APACHE II score			
N	101	49	150
Mean	15.3	15.4	15.3
Standard deviation	6.5	6.2	6.4
Median	15.0	14.0	15.0
Minimum	2	2	2
Maximum	29	28	29
Total APACHE II score group (n, %)			
≤ 15	55 (54.5)	27 (55.1)	82 (54.7)
≥ 16	46 (45.5)	22 (44.9)	68 (45.3)

	<b>Cefiderocol (N = 101)</b>	<b>BAT (N = 49)</b>	<b>Total (N = 150)</b>
<b>Weight (kg)</b>			
N	101	49	150
Mean	70.28	70.74	70.43
Standard deviation	22.01	20.23	21.38
Median	68.90	65.00	67.85
Minimum	25.0	30.0	25.0
Maximum	156.0	127.0	156.0
<b>Weight group (n, %)</b>			
< 70 kg	53 (52.5)	27 (55.1)	80 (53.3)
≥ 70 kg	48 (47.5)	22 (44.9)	70 (46.7)
<b>Height (cm)</b>			
N	99	49	148
Mean	165.52	167.18	166.07
Standard deviation	11.34	9.65	10.80
Median	165.00	170.00	167.00
Minimum	118.0	141.0	118.0
Maximum	190.0	182.9	190.0
<b>Body mass index (kg/m<sup>2</sup>)</b>			
N	99	49	148
Mean	25.46	25.32	25.41
Standard deviation	6.91	7.25	7.00
Median	24.95	23.51	24.45
Minimum	12.0	14.3	12.0
Maximum	52.4	48.9	52.4
<b>Creatinine clearance (mL/min) [a]</b>			
N	101	49	150
Mean	85.77	88.87	86.78
Standard deviation	79.33	64.20	74.53
Median	59.22	69.44	63.39
Minimum	9.4	4.6	4.6
Maximum	539.6	270.8	539.6
<b>Creatinine clearance renal grading group (n, %) [a]</b>			
≥ 120 mL/min (ARC)	20 (19.8)	12 (24.5)	32 (21.3)
> 80 mL/min to < 120 mL/min (normal)	18 (17.8)	10 (20.4)	28 (18.7)
> 50 mL/min to 80 mL/min (mild)	20 (19.8)	12 (24.5)	32 (21.3)
30 mL/min to 50 mL/min (moderate)	23 (22.8)	8 (16.3)	31 (20.7)
< 30 mL/min (severe)	20 (19.8)	7 (14.3)	27 (18.0)
<b>Clinical diagnosis at baseline (n, %)</b>			
HAP/VAP/HCAP	45 (44.6)	22 (44.9)	67 (44.7)
HAP	20 (19.8)	7 (14.3)	27 (18.0)
VAP	24 (23.8)	13 (26.5)	37 (24.7)
HCAP	1 (1.0)	2 (4.1)	3 (2.0)

	<b>Cefiderocol (N = 101)</b>	<b>BAT (N = 49)</b>	<b>Total (N = 150)</b>
BSI/Sepsis	30 (29.7)	17 (34.7)	47 (31.3)
BSI	22 (21.8)	9 (18.4)	31 (20.7)
cIAI	3 (3.0)	2 (4.1)	5 (3.3)
SSSI	1 (1.0)	0	1 (0.7)
Intravenous line	4 (4.0)	2 (4.1)	6 (4.0)
Other	5 (5.0)	1 (2.0)	6 (4.0)
Unknown	9 (8.9)	4 (8.2)	13 (8.7)
Sepsis	8 (7.9)	8 (16.3)	16 (10.7)
cIAI	2 (2.0)	1 (2.0)	3 (2.0)
SSSI	4 (4.0)	3 (6.1)	7 (4.7)
Intravenous line	0	3 (6.1)	3 (2.0)
Other	2 (2.0)	1 (2.0)	3 (2.0)
cUTI	26 (25.7)	10 (20.4)	36 (24.0)
Severity of disease (n, %)			
Mild	5 (5.0)	4 (8.2)	9 (6.0)
Moderate	41 (40.6)	22 (44.9)	63 (42.0)
Severe	55 (54.5)	23 (46.9)	78 (52.0)
Baseline fever (n, %)			
≥ 38.0 grade Celsius	14 (13.9)	7 (14.3)	21 (14.0)
< 38.0 grade Celsius	86 (85.1)	40 (81.6)	126 (84.0)
Medical history (n, %)			
Yes	101 (100.0)	49 (100.0)	150 (100.0)
Prior therapy (n, %) [b]			
No	8 (7.9)	0	8 (5.3)
Yes	93 (92.1)	49 (100.0)	142 (94.7)
Number of Gram-negative pathogens from appropriate specimen at baseline (n, %) [c]			
0	15 (14.9)	5 (10.2)	20 (13.3)
1	68 (67.3)	36 (73.5)	104 (69.3)
2	13 (12.9)	8 (16.3)	21 (14.0)
3	4 (4.0)	0	4 (2.7)
4	1 (1.0)	0	1 (0.7)
Sequential Organ Failure Assessment Score (SOFA)			
N	100	49	149
Mean	5.1	5.1	5.1
Standard deviation	4.0	3.8	3.9
Median	4.0	4.0	4.0
Minimum	0	0	0
Maximum	17	16	17

	<b>Cefiderocol (N = 101)</b>	<b>BAT (N = 49)</b>	<b>Total (N = 150)</b>
<b>Clinical Pulmonary Infection Score (CPIS) [d]</b>			
N	44	21	65
Mean	4.9	4.6	4.8
Standard deviation	1.7	1.5	1.6
Median	5.0	5.0	5.0
Minimum	2	0	0
Maximum	9	7	9

APACHE II = Acute Physiology and Chronic Health Evaluation II; ARC = augmented renal clearance; BAT = best available therapy; BSI = bloodstream infection; cIAI = complicated intra-abdominal infections; cUTI = complicated urinary tract infection; HAP = hospital-acquired pneumonia; HCAP = healthcare-associated pneumonia; SSSI = skin and skin structure infection; VAP = ventilator-associated pneumonia

Percentage was calculated using the number of subjects in the column heading as the denominator.

- [a] Creatinine clearance was calculated using the Cockcroft-Gault formula  $[(140 - \text{age in years}) \times (\text{actual weight in kg})] / (72 \times \text{serum creatinine in mg/dL})$ ; multiply by 0.85 if female] based on data from the central laboratory.
- [b] Prior antimicrobial therapy taken 2 weeks prior to randomization.
- [c] Appropriate specimen as defined in the protocol.
- [d] Only collected from subjects with HAP/VAP/HCAP.

## 15.4 Appendix 4 – CREDIBLE-CR Study Clinical Outcomes Definitions (Infection Site Specific)

Timepoint	Clinical Outcomes	Infection Site		
		HAP/VAP/HCAP	cUTI	BSI/Sepsis
EA, EOT, and TOC	Clinical cure	Resolution or substantial improvement of baseline signs and symptoms of pneumonia, including a reduction in SOFA score and CPIS, and improvement or lack of progression of chest radiographic abnormalities such that no antibacterial therapy was required for the treatment of the current infection.	Resolution or substantial improvement of baseline signs and symptoms of cUTI, or return to preinfection baseline if known, such that no antibacterial therapy was required for the treatment of the current infection.	Resolution or substantial improvement of baseline signs and symptoms including a reduction in SOFA score, such that no antibacterial therapy was required for the treatment of BSI/sepsis. Subjects with bacteremia must have had eradication of bacteremia caused by the Gram-negative pathogen.
	Clinical failure	No apparent response to therapy; persistence or worsening of baseline signs and/or symptoms of pneumonia; reappearance of signs and/or symptoms of pneumonia; development of new signs and/or symptoms of pneumonia requiring antibiotic therapy other than, or in addition to, study treatment therapy; progression of chest radiographic abnormalities; or death due to pneumonia.	No apparent response to therapy; persistence or worsening of baseline signs and/or symptoms of cUTI; or reappearance of signs and/or symptoms of cUTI; development of new signs and/or symptoms of cUTI requiring antibiotic therapy other than, or in addition to, study treatment therapy; or death due to cUTI.	No apparent response to therapy; persistence or worsening of baseline signs and/or symptoms, reappearance of signs and/or symptoms; development of new signs and/or symptoms requiring antibiotic therapy other than, or in addition to, study treatment therapy; or death due to BSI/sepsis.
	Indeterminate	Lost to follow-up such that a determination of clinical cure/failure could not be made.		

Timepoint	Clinical Outcomes	Infection Site		
		HAP/VAP/HCAP	cUTI	BSI/Sepsis
Follow-up	Sustained clinical cure	Continued resolution or improvement of baseline signs and symptoms of pneumonia, such that no antibacterial therapy was required for the treatment of pneumonia in a subject assessed as cured at TOC.	Continued resolution or improvement of baseline signs and symptoms of cUTI, or return to preinfection baseline if known, in a subject assessed as cured at TOC	Continued resolution or substantial improvement of baseline signs and symptoms associated with reduction in SOFA score, such that no antibacterial therapy was required for the treatment of the subject's original BSI/sepsis in a subject assessed as cured at TOC.
	Clinical failure:	Clinical failure at TOC was carried forward.		
	Relapse	Recurrence of signs and/or symptoms of pneumonia, appearance of new signs and/or symptoms of pneumonia, new chest radiographic evidence of pneumonia, or death due to pneumonia in a subject assessed as cured at TOC.	Recurrence of signs and/or symptoms of cUTI, or appearance of new signs and/or symptoms of cUTI in a subject assessed as cured at TOC	Recurrence of signs and/or symptoms of BSI/sepsis, appearance of new signs and/or symptoms of the subject's original BSI/sepsis, or death due to BSI/sepsis in a subject assessed as cured at TOC.
	Indeterminate	Lost to follow-up such that a determination of clinical sustained cure/relapse could not be made, or subject received additional antibacterial therapy for the treatment of the current infection.		

BSI = bloodstream infection; CPIS = Clinical Pulmonary Infection Score; cUTI = complicated urinary tract infection; EA = Early Assessment; EOT = End of Treatment; HAP = hospital-acquired pneumonia; HCAP = healthcare-associated pneumonia; SOFA = Sequential Organ Failure Assessment; TOC = Test of Cure; VAP = ventilator-associated pneumonia

## 15.5 Appendix 5 – CREDIBLE-CR Study Microbiological Outcomes Definitions (Infection Site Specific)

Timepoint	Microbiological Outcomes	Infection Site		
		HAP/VAP/HCAP	cUTI	BSI/Sepsis
EA, EOT, and TOC	Eradication	Absence of the baseline Gram-negative pathogen from an appropriate clinical specimen. If it was not possible to obtain an appropriate clinical culture and the subject had a successful clinical outcome, the response was presumed to be eradication.	A urine culture showed the baseline Gram-negative uropathogen found at entry at $\geq 10^5$ CFU/mL was reduced to $< 10^3$ CFU/mL.	Absence of the baseline Gram-negative pathogen from a blood culture and/or other primary source as applicable. In the case of sepsis, if the subject had a successful clinical outcome and it was not possible to obtain an appropriate clinical culture, the response was presumed to be eradication. In the case of BSI, if the subject has a successful clinical outcome and the investigator considers no further need to obtain a clinical culture, the response was presumed to be eradication.
	Persistence	Continued presence of the baseline Gram-negative pathogen from an appropriate clinical specimen.	A urine culture showed that the baseline Gram-negative uropathogen found at entry at $\geq 10^5$ CFU/mL grew to $\geq 10^3$ CFU/mL.	Continued presence of the baseline Gram-negative pathogen from a blood culture or other primary source.
	Indeterminate	No culture <sup>a</sup> obtained from an appropriate clinical specimen or additional antibacterial therapy for the treatment of the current infection including missed sampling.		

Timepoint	Microbiological Outcomes	Infection Site		
		HAP/VAP/HCAP	cUTI	BSI/Sepsis
Follow-up	Sustained eradication	Absence of the baseline Gram-negative pathogen from an appropriate clinical specimen after TOC. If it was not possible to obtain an appropriate clinical culture and the subject had a successful clinical response after TOC, the response was presumed eradication.	A culture taken any time after documented eradication at TOC and a urine culture obtained at FU showed that the baseline uropathogen found at entry at $\geq 10^5$ CFU/mL remained $< 10^3$ CFU/mL.	Absence of the baseline Gram-negative pathogen from a blood culture or other primary source after TOC as applicable. In the case of sepsis, if the subject had a successful clinical outcome after TOC and it was not possible to obtain an appropriate clinical culture, the response was presumed to be sustained eradication. In the case of BSI, if the subject has a successful clinical outcome and the investigator considers no further need to obtain a clinical culture, the response was presumed to be eradication
	Persistence	Persistence at TOC was carried forward.		
	Recurrence	Recurrence of the baseline Gram-negative pathogen from an appropriate clinical specimen taken after TOC, and the TOC culture was negative.	A culture taken any time after documented eradication at TOC, up to and including FU that grew the baseline uropathogen $\geq 10^3$ CFU/mL.	Recurrence of the baseline Gram-negative pathogen from a blood culture or other primary source after TOC, and the TOC culture was negative.
	Indeterminate	No culture obtained from an appropriate clinical specimen or subject received additional antibacterial therapy for the treatment of the current infection including missed sampling.	No urine culture or subject received additional antibacterial therapy for the treatment of the current infection including missed sampling.	No culture or subject received additional antibacterial therapy for the treatment of the current infection including missed sampling.

BSI = bloodstream infection; CFU = colony-forming units; cUTI = complicated urinary tract infection; EA = Early Assessment; EOT = End of Treatment; FU = follow-up; HAP = hospital-acquired pneumonia; HCAP = healthcare-associated pneumonia; TOC = Test of Cure; VAP = ventilator-associated pneumonia

a Urine culture specified for cUTI.

## 15.6 Appendix 6 – Summary of Liver Events (Severe or Drug Related)

### **CREDIBLE-CR Study - Summary of Liver events considered severe or considered related to Study Drug:**

- Two subjects (Patients # 44 and #29) had mild/moderate AEs of ALT and AST increased, which were considered by the investigator as related to study drug. ALT and AST increased reported for Patient # 44 were recovering before the subject became lost to follow-up after TOC. Patient # 29 had a medical history of hepatitis B ongoing at the time of randomization and died on Day 18 due to VAP and bacteremia.
- One Subject (Patient # 33) had severe AEs of ALT and AST increased, which were considered by the investigator as related to study drug. ALT and AST increased were recovered while continuing to receive Cefiderocol.
- One subject (Patient # 16) had a mild AE of AST increased, which was considered by the investigator as related to study drug. Administration of co-suspect fosfomycin suggested an alternate etiology. AST and ALT levels also transiently decreased while continuing to receive study drug.
- One subject (Patient # 45) had a severe AE of AST increased on Day 15, 7days after EOT; the AE of AST increased resolved on Day 36.
- One subject (Patient # 13) had a severe AE of worsening of hepatitis, which was considered not related to the study drug; this subject had a medical history of cholangiocarcinoma and hepatitis considered due to cholangiocarcinoma, which were ongoing at the time of randomization. Patient # 13 died on Day 9 due to septic shock.
- One subject (Patient # 27) had severe AEs of hepatic cirrhosis and hepatic failure, which were considered by the investigator as not related to the study drug and hepatic failure was fatal. Patient # 27 had medical history of advanced liver cirrhosis with hepatic encephalopathy, oesophageal varices haemorrhage, and hepatic failure, which were ongoing at the time of randomization.
- Two subjects (Patient # 18 and Patient # 21) had severe AEs of Liver function test abnormal, which were considered not related to the study drug.

Patient # 18 with underlying jaundice, cholelithiasis, intermittent abnormal AST and ALT levels, acute renal failure and elevated bilirubin levels at baseline received cefiderocol. On day 6 the subject experienced serious lower GI hemorrhage and on day 8 experienced intestinal ischemia and large intestinal perforation. On day 11 abnormal LFT levels were observed which met also seriousness criteria. On day 13, enterococcal bacteremia occurred and the study drug was discontinued. On day 30, 17 days after the last dose, the subject died due to multi-organ failure and septic shock. The underlying jaundice, elevated bilirubin levels at baseline and concomitant administration of metoclopramide and blood transfusions, and septic shock suggest an alternate. Patient # 21 with

underlying rectal cancer with metastasis to the liver, lungs, brain and left arm received cefiderocol. The subject experienced serious events of septic shock on day 4 and LFT increase and cardiac arrest on day 5 and died the same day. Cause of death was reported as septic shock. Rectal cancer with liver metastasis, elevated bilirubin levels at baseline and underlying sepsis suggest alternate etiologies for the LFT increase.

- One subject (Patient # 46) had severe AEs of Transaminases increased, which was considered by the investigator as related to the study drug. Patient # 46 with underlying ischemic heart disease received cefiderocol. On day 5 the subject experienced serious transaminases increased and discontinued the study drug. The event was recovered after discontinuation. A blood transfusion which is also known to increase liver enzymes was administered 2 days prior suggesting an alternate etiology.

### **CREDIBLE-CR Study - Patients with Treatment-emergent Drug-related Hepatic Disorders Adverse Events by Standard MedDRA Queries and Preferred Term (Safety Population)**

<b>Standard MedDRA Queries - Preferred Term</b>	<b>CREDIBLE-CR Study</b>	
	<b>Cefiderocol N=101 n (%)</b>	<b>BAT N=49 n (%)</b>
Drug related hepatic disorders - comprehensive search	30 (29.7)	7 (14.3)
- Alanine aminotransferase increased	7 (6.9)	0
- Aspartate aminotransferase increased	8 (7.9)	1 (2.0)
- Liver function test abnormal	8 (7.9)	4 (8.2)
- Gamma-glutamyltransferase increased	2 (2.0)	0
- Ascites	2 (2.0)	0
- Blood bilirubin increased	2 (2.0)	1 (2.0)
- Hepatic function abnormal	2 (2.0)	0
- Hypoalbuminaemia	2 (2.0)	0
- International normalised ratio increased	2 (2.0)	1 (2.0)
- Blood alkaline phosphatase increased	2 (2.0)	0
- Hepatic cirrhosis	1 (1.0)	0
- Hepatic failure	1 (1.0)	0
- Hepatitis	1 (1.0)	0
- Hepatocellular injury	1 (1.0)	0
- Hepatomegaly	1 (1.0)	0
- Hyperbilirubinaemia	1 (1.0)	0
- Transaminases increased	1 (1.0)	0
- Chronic hepatic failure	1 (1.0)	0
- Hepatic enzyme increased	0	1 (2.0)

BAT = best available therapy

Adverse events are coded using MedDRA Version 19.0.

**CREDIBLE-CR Study: Number (%) of Patients With Abnormal Liver Chemistry Values Meeting Predefined Outlier Limits Postbaseline (Safety Population)**

<b>Parameter (Unit)</b>	<b>Cefiderocol (N = 101)</b>	<b>BAT (N = 49)</b>
<b>Category</b>	<b>n (%)</b>	<b>n (%)</b>
AST (U/L)	N' = 96	N' = 48
Value > 3 × ULN	20 (20.8)	7 (14.6)
Value > 5 × ULN	11 (11.5)	7 (14.6)
Value > 10 × ULN	6 (6.3)	1 (2.1)
ALT (U/L)	N' = 98	N' = 48
Value > 3 × ULN	16 (16.3)	4 (8.3)
Value > 5 × ULN	5 (5.1)	3 (6.3)
Value > 10 × ULN	1 (1.0)	2 (4.2)
AST (U/L) or ALT (U/L)	N' = 96	N' = 48
Value > 3 × ULN	25 (26.0)	8 (16.7)
Value > 5 × ULN	12 (12.5)	7 (14.6)
Value > 10 × ULN	6 (6.3)	3 (6.3)
Total bilirubin (μmol/L)	N' = 93	N' = 48
Value > 2 × ULN	14 (15.1)	6 (12.5)
(ALT and/or AST > 3 × ULN) and (Total bilirubin > 2 × ULN or PT-INR > 1.5)	N' = 91	N' = 46
	12 (13.2)	4 (8.7)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BAT = best available therapy; INC = increase from baseline; PT-INR = prothrombin time-international normalized ratio; ULN = upper limit of normal

Percentage was calculated using N' as the denominator, where N' was the number of subjects with valid postbaseline measurements. The summary was based on local laboratory assessments and the data that could be converted into standard unit.

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## **15.7 Appendix 7 – Detailed Narratives of Patient Deaths Adjudicated to be Due to Baseline Gram-negative Pathogen (Category 2)**

## Subject ID Patient # 17

Subject ID	Patient # 17	Country	Spain			
Age	92	Clinical Diagnosis at Screening	cUTI			
Gender	Male	Severity	Severe			
Race	White	APACHE II Score	11			
Height (cm)	160.0	Causative Pathogen at Screening	<i>Klebsiella pneumoniae</i>			
Body Weight (kg)	55.0	CR Evidence at Screening (other than central lab)	Positive rapid diagnostic test (Rapidec Carba NP)			
MIC of Meropenem	64 µg/mL	MIC of Cefiderocol	1 µg/mL			
MIC of Imipenem	32 µg/mL					
Duration of Study Treatment	4 days	Standard of Care	Ceftazidime-avibactam (1 g IV)			
Study Drug Treatment	Cefiderocol (2 g q8h IV)					
Microbiological Results at TOC		Day 28 All-cause Mortality	Clinical Outcome at TOC			
Indeterminate		Death (on Day 4)	Indeterminate			
Medical History (Ongoing)	Arterial hypertension, hypercholesterolemia, COPD, AF, polyarthritis, chronic anemia, bilateral hip prosthesis, chronic venous insufficiency, constipation, Raynaud's syndrome					
Medical History (Not Ongoing)	Gastrectomy, cholecystectomy; ischemic cardiomyopathy; TIA					
Adverse Event	Day	Severity	Action Taken with Study Drug	Outcome	Causality	Serious
Anorexia	2	Moderate	Dose not changed	Not recovered/ not resolved	Not related	No
Nausea	3	Moderate	Dose not changed	Not recovered/ not resolved	Not related	No
Vomiting	3	Moderate	Dose not changed	Not recovered/ not resolved	Not related	No
Hypotension	3	Severe	Dose not changed	Fatal	Not related	Yes
Oliguria	3	Severe	Dose not changed	Fatal	Not related	Yes
Indeterminate refractory shock	3	Severe	Dose not changed	Fatal	Not related	Yes
Progressive failure of the organs	3	Severe	Dose not changed	Fatal	Not related	Yes

### Narrative Summary

A 92-year-old white male from Spain had a history of COPD, AF, TIA, and ischemic cardiomyopathy developed cUTI on Day -5. He was bedridden. Gentamicin was administered from Days -8 to -6; IV fosfomycin was administered from Days -7 to -4 and then switched to oral fosfomycin from Days -4 to -3.

He was admitted from home to the study site on Day -1 due to KPC-producing cUTI. Rapid diagnostic test (Rapidec Carba NP) was positive for the urine specimen on the day of admission and he was enrolled in the study on Day 1. The urine sample collected (indwelling catheter) isolated *K. pneumoniae* (quantitation,  $> 1.0 \times 10^5$  CFU/mL) on Day 3. Blood culture was negative (Day 1).

The patient was assigned to the cefiderocol arm and received 2 g q8h IV from Days 1 to 4 (total of 8 doses). On Day 3, the patient started to complain of moderate nausea and severe fatigue in the morning (Day 1) and developed the SAEs of unrelated hypotension and unrelated oliguria on Day 3. Fluid resuscitation and dopamine were started.

Laboratory data demonstrated a high D Dimer. The SAEs of unrelated indeterminate refractory shock and progressive failure of organs were reported. The patient did not respond to resuscitation or vasopressors. A CT scan was performed at 19:38 hours to rule out mesenteric ischemia, aortic aneurysm, intestinal obstruction, bowel perforation, or other abdominal causes of shock. However, the findings were nonspecific and showed generalized subcutaneous edema, discrete bilateral pleural perfusion, posterior right basal atelectasis/consolidation, old left posterior costal fractures, abundant fecal material, no significant dilatation of the intestinal loops, no signs and/or symptoms of pneumatosis, gastric distention, left suprarenal nodule (25 mm) suggestive of incidental adenoma, normal kidneys with isolated cysts, generalized vascular calcifications, already known articular destruction of right hip, and left hip prosthesis. The patient's family did not want the patient be admitted to the ICU and asked not to perform the additional complementary explorations that were pending. The patient died on Day 4 at 02:30 hours.

AF = atrial fibrillation; APACHE = Acute Physiology and Chronic Health Evaluation; CFU = colony-forming units; COPD = chronic obstructive pulmonary disease; CR = carbapenem resistance; CT = computed tomography; cUTI = complicated urinary tract infection; EOT = End of Treatment; ICU = intensive care unit; ID = identification; IV = intravenous; KPC = *K. pneumoniae* carbapenem; MIC = minimum inhibitory concentration; q8h = every 8 hours; SAE = serious adverse event; TIA = transient ischemic attack; TOC = Test of Cure; unk = unknown

**Study qualifying diagnosis:** Complicated urinary tract infection due to *K. pneumoniae* with evidence of CR through a positive rapid diagnostic test (Rapidec Carba NP).

**Study qualifying infection history:** On Day -1, a urine sample showed *K. pneumoniae* resistant to amikacin, aztreonam, cefepime, ceftolozane-tazobactam, ciprofloxacin, imipenem, and meropenem. The isolate was susceptible to colistin and ceftazidime-avibactam and had intermediate sensitivity to tigecycline (Table 3).

**Current hospitalization history:** Complicated urinary tract infection onset was Day -5. The patient was hospitalized as an elective admission on Day -8 and received IV gentamicin from Day -8 to Day -6 and IV fosfomycin from Day -7 to Day -4. The patient was discharged on Day -4 and received oral fosfomycin from Day -4 to Day -3. On Day -1, the patient was hospitalized again as an elective admission from home due to the current infection.

**Clinical course:** Treatment with cefiderocol 2 g q8h IV was initiated on Day 1. He received 7 subsequent infusions of cefiderocol from Day 2 to Day 4. The last infusion of cefiderocol was interrupted on Day 4.

On Day -1, a microbiological laboratory specimen was obtained from the urine via an indwelling catheter. Gram-negative rods (+) were identified. The pathogen *K. pneumoniae* (quantitation,  $> 1 \times 10^5$ ; no quantitation, heavy growth) was identified.

On Day 1 (Screening/Baseline), a microbiological laboratory specimen was obtained from the blood. The blood culture was negative for both Gram-negative rods and pathogens. The initial clinical assessment was performed and moderate dysuria and suprapubic/flank/back pain, and severe fatigue and malaise were noted. The Sequential Organ Failure Assessment (SOFA) score was 1 (Table 2). The inflammatory indices of white blood cell (WBC) count, C-reactive protein (CRP), and body temperature were  $5.98 \times 10^9/L$ , 49.43 mg/L, and 36.1°C, respectively (Table 1).

On Day 3, the patient experienced the SAEs of hypotension, oliguria, indeterminate refractory shock, and progressive failure of the organs. His vital signs were 72/52 mm Hg and 35.0°C (hypothermic, 08:15 hours), and 80/40 mm Hg and 36.4°C (23:30 hours). Treatment included 1000 cc of 0.9% physiological saline, dopamine drip for hypotension, metoclopramide 10 mg IV q8h for vomiting and nausea, and morphine 5 mg continuous IV for progressive failure of the organs. Laboratory data demonstrated high D Dimer (1870 ng/mL [reference range (RR) = 0 to 500]). Platelets were  $138 \times 10^3/\mu L$  (RR = 130 to 450). Other laboratory data was unremarkable (leukocytes were  $9.850 \times 10^9/L$  [RR = 4 to 12], hemoglobin was 11.4 g/dL [RR = 12 to 18], creatinine was 1.2  $\mu\text{mol/L}$  [RR = 0.5 to 1.1], urea was 62 mg/dL [RR = 20 to 50], total bilirubin was 0.2 mg/dL [RR = 0.3 to 1.2], aspartate aminotransferase [AST] was 18 U/L [RR = 5 to 34], alanine aminotransferase [ALT] was 12 U/L [RR = 10 to 49 U/L], lactate dehydrogenase [LDH] was 194 U/L [RR = 125 to 220 U/L], creatine kinase [CK] was 23 U/L [RR = 32 to 211], and coagulation test was normal). Blood and urine cultures were not taken on Day 3. The patient did not respond to resuscitation and vasopressors. However, the findings were nonspecific and showed generalized subcutaneous edema, discrete bilateral pleural perfusion, posterior right basal atelectasis/consolidation, old left posterior costal fractures, abundant fecal material, no significant dilatation of the intestinal loops, no signs and/or symptoms of pneumatosis, gastric distention, left suprarenal nodule (25 mm) suggestive of incidental adenoma, normal kidneys with isolated cysts, generalized vascular calcifications, already known articular destruction of right hip, and left hip prosthesis. The patient's family asked that the patient not be admitted to the ICU and asked not to perform the additional complementary explorations that were pending. The investigator considered the events severe and not related to study medication. The patient died due to the events on Day 4 at 02:30 hours.

**Table 1 Inflammatory Indices**

Visit	White Blood Cell Count (RR = 4 to 12)	C-reactive Protein (RR = 0 to 10)	Body Temperature
Screening/Baseline	$5.98 \times 10^9/L$	49.43 mg/L	36.1°C

RR = reference range

**Table 2 Sequential Organ Failure Assessment Status**

Visit	SOFA Score
Screening/Baseline	1

SOFA = Sequential Organ Failure Assessment

**Table 3 Antimicrobial Susceptibility Testing at Screening  
(European Committee on Antimicrobial Susceptibility  
Testing)**

Pathogen	Resistant	Intermediate	Susceptible	Not Applicable
<i>Klebsiella pneumoniae</i>	Amikacin, aztreonam, cefepime, ceftolozane-tazobactam, ciprofloxacin, imipenem, meropenem	Tigecycline	Colistin, ceftazidime-avibactam	Cefiderocol

**Table 4 Susceptibility Testing at Each Visit**

Visit	IHMA Organism ID	AMK	AZT	CFPM	CAZ/AVI	CEF/TAZ	CPFX	CST	IPM	MEPM	CFDC	TGC
		MIC µg/mL										
Screening/ Baseline	<i>Klebsiella pneumoniae</i> Sample ID E690122	32	> 32	> 16	0.5	64	> 4	1	32	64	1	2

AMK = amikacin; AZT = aztreonam; CAZ/AVI = ceftazidime-avibactam; CEF/TAZ = ceftolozane-tazobactam; CFDC = cefiderocol; CFPM = cefepime; CPFX = ciprofloxacin; CST = colistin; ID = identification; IHMA = International Health Management Associates; IPM = imipenem; MEPM = meropenem; MIC = minimum inhibitory concentration; TGC = tigecycline

**Table 5 Liver Function Tests**

Visit	AST (RR = 5 to 34)	ALT (RR = 10 to 49)	ALP (RR = 46 to 116)	GGT (RR = 3 to 60)	Total Bilirubin (RR = 0.3 to 1.2)
Screening/Baseline	12 U/L	< 9 U/L	62 U/L	10 U/L	0.4 mg/dL

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase;  
GGT = gamma-glutamyl transferase; RR = reference range

**Table 6 Renal Function Tests**

Visit	Blood Urea Nitrogen (RR = 20 to 50)	Serum Creatinine (RR = 0.5 to 1.1)	Creatinine Clearance (RR = NA)
Screening/Baseline	37.33 mg/dL	1.03 mg/dL	35.60 mL/min

NA = not available; RR = reference range

**Table 7 Coagulation Tests**

Visit	Platelet Count (RR = 130 to 450)	aPTT (RR = 30 to 40)	PT-INR (RR = 0.9 to 1.3)
Screening/Baseline	$115 \times 10^3/\mu\text{L}$	28.3 sec	1.3

aPTT = activated partial thromboplastin time; PT-INR = prothrombin international normalized ratio;  
RR = reference range

## Subject ID Patient # 18

Subject ID		Patient # 18	Country		Greece	
Age		78	Clinical Diagnosis at Screening		HAP	
Gender		Male	Severity		Moderate	
Race		White	APACHE II Score		17	
Height (cm)		167.0	Causative Pathogen at Screening		Acinetobacter baumannii; Klebsiella pneumoniae	
Body Weight (kg)		84.0	CR Evidence at Screening (other than central lab)		Treatment failure CR-GNB	
MIC of Meropenem		> 64 µg/mL, A. baumannii; 16 µg/mL, K. pneumoniae	MIC of Cefiderocol		0.5 µg/mL, A. baumannii; 0.25 µg/mL, K. pneumoniae	
MIC of Imipenem		64 µg/mL, A. baumannii; 32 µg/mL, K. pneumoniae				
Duration of Study Treatment		14 days	Standard of Care		Ampicillin/sulbactam (9 g, q6h, IV) Tigecycline (100 mg, q12h, IV)	
Study Drug		Cefiderocol 1.5 g q12h IV				
Microbiological Results at TOC			Day 28 All-cause Mortality		Clinical Outcome at TOC	
Persistence			Death (Day 31)		Clinical failure	
Medical History (Ongoing)	Coagulopathy-increased INR, jaundice, abnormal liver function tests with elevated SGOT; acute renal failure requiring CVVHDF					
Medical History (Not Ongoing)	Ruptured abdominal aortic aneurysm, emergency surgery for the ruptured abdominal aortic aneurysm					
Adverse Event	Day	Severity	Action Taken with Study Drug	Outcome	Causality	Serious
Bleeding from oral cavity ulcer	5	Moderate	Dose not changed	Recovered/resolved	Not related	No
Lower gastrointestinal bleeding	7	Severe	Dose not changed	Recovering/resolving	Not related	Yes
Hiccup	8	Mild	Dose not changed	Recovered/resolved	Not related	No
Descending colon, sigmoid colon and rectum ischemia leading to perforation and peritonitis	9	Severe	Dose not changed	Not recovered/Not resolved	Not related	Yes

Abnormal liver function tests worsening	12	Severe	Dose not changed	Not recovered/ Not resolved	Not related	Yes
<i>Enterococcus faecium</i> bacteremia	14	Severe	Dose not changed	Recovered/ resolved	Not related	Yes
Thrombocytopenia	16	Moderate	NA	Not recovered/ Not resolved	Not related	No
Empyema	19	Severe	NA	Not recovered/ Not resolved	Not related	Yes
Pneumothorax	23	Mild	NA	Recovering/ resolving	Not related	No
Septic shock	29	Severe	NA	Fatal	Not related	Yes

#### **Narrative Summary**

A 78-year-old white male from Greece had a medical history of ruptured AAA, emergency surgery for the ruptured AAA (Day -11), jaundice, abnormal liver function tests with elevated SGOT, coagulopathy-increased INR (Day -10), and acute renal failure requiring CVVHDF (Day -9).

On Day -11, the patient had an acute rupture of AAA and underwent emergency surgery. Metronidazole was provided from Day -10 to -8. Piperacillin with tazobactam and daptomycin was provided until Day -5. The investigator reported that the patient was hemodynamically stable, in ICU, intubated and attached to mechanical ventilation on Day -11. After a short period of time, the patient was able to breathe without mechanical support and was placed on a T-piece. He remained intubated during hospitalization and was never extubated. While on the T-piece, he developed pneumonia from *A. baumannii* (HAP). The TA culture showed *A. baumannii* resistant to carbapenems (cultured Day -2 and resulted Day 1). On Day 1, patient was started on treatment with ampicillin/sulbactam; on Day 6, treatment was changed to tigecycline, as adjunctive antibiotics for Gram-negative coverage along with the study treatment, cefiderocol (randomized treatment).

On Day 1, the patient was enrolled in the study with the diagnosis of HAP. The patient's baseline SOFA score was 9, and his CPIS was 9. Chest x-ray showed right mid-lower lung field consolidation with increased density on all left lung fields with no significant abnormality of heart/vessels. Evidence of CR was reported on TA, and he was enrolled in the study via treatment failure pathway. TA culture collected on Day -2 was positive for *A. baumannii* (results on Day 1). The TA culture obtained on Day 1 (results available on Day 3) showed *A. baumannii*, *K. pneumoniae*, and *Escherichia coli*.

The patient was randomized to cefiderocol at a dose of 1.5 g q12h from Days 1 to 14.

On Day 4, EA was performed. Chest x-ray showed no change in comparison to Baseline evaluation of lung fields. The TA culture was negative.

On Day 7, the patient developed the unrelated SAE of lower gastrointestinal bleeding, (severe), which led to anemia requiring 2 units of RBC. The SAE was diagnosed with colonoscopy which revealed bowel ischemia with regions of necrosis.

On Day 9, a CT scan (with gastrografin administered via feeding tube) showed intestinal perforation. The unrelated SAE of descending colon, sigmoid colon, and rectum ischemia leading to perforation and peritonitis was reported. A laparotomy was performed with excision of the descending colon, sigmoid colon, and rectum. The SAE was considered a consequence of the AAA rupture.

On Day 12, the investigator reported the patient's worsening of abnormal liver function tests (TBL elevation that was due to a sepsis-like clinical condition) was reported as SAEs.

On Day 14, the EOT assessment was performed. The chest x-ray did not show any changes compared to baseline but showed diffuse opacity of all fields on the left lung and patchy infiltrates of the lower fields on the right lung. The TA culture showed *A. baumannii*, *P. aeruginosa*, and *K. pneumoniae*. Clinical and microbiological outcomes showed clinical cure and persistence, respectively.

The unrelated SAE of *E. faecium* bacteremia was reported (Day 14). On Day 16, the event of thrombocytopenia (moderate) was reported. Daptomycin was started (Day 17) and provided until Day 27. The low platelet count was attributed to the septic episode that followed colon ischemia, perforation and peritonitis as per the investigator. Outcome for the event of thrombocytopenia was reported as not recovered/not resolved. On Day 19, an unscheduled visit, pleural fluids were positive for *P. aeruginosa* (no quantitation; resulted on Day 21).

The SAE of empyema was reported on Day 19; outcome was reported as not recovered/not resolved. The investigator reported the causality to be not related to study drug for the SAE of empyema.

There was no improvement of his general clinical/laboratory status and an abdominal CT revealed pleural fluid in the left lung. A diagnostic puncture showed collection of pus in the pleural cavity.

On Day 23, the TOC assessment was completed. Chest x-ray showed worsened diffuse infiltrations of all pulmonary fields, bilaterally. The TA culture was positive for *P. aeruginosa* and *K. pneumoniae* (Day 23). The outcomes were assessed as clinical failure with microbiological persistence. On the same day, the mild unrelated AE of pneumothorax was reported, iatrogenic pneumothorax due to subclavicular needle stick was reported and management included chest tube placement.

On Day 25, Follow-up visit, chest x-ray showed diffuse infiltrates on both lungs, predominately in lower lung fields and the presence of 2 chest tubes on the right lung with subcutaneous emphysema. The outcome of the SAE of *E. faecium* bacteremia was reported as recovered/resolved on Day 25. The TA culture was positive on Day 25, and *P. aeruginosa*, *Stenotrophomonas maltophilia*, and *K. pneumoniae* were identified. Clinical outcome was assessed as failure and microbiological outcome was assessed as sustained persistence.

On Day 29, the patient's condition deteriorated with worsening hemodynamic status, and increased need for fluid administration; new antibiotic treatment was started with vancomycin (Day 27) until Day 31. The SAE of septic shock was reported on Day 29 and the outcome of the event was fatal. The investigator reported the causality as not related to study drug.

On Day 31, the patient died due to septic shock, 17 days after receiving his last dose of study medication.

AAA = abdominal aortic aneurysm; AE = adverse event; APACHE = Acute Physiology and Chronic Health Evaluation; CPIS = Clinical Pulmonary Infection Score; CR = carbapenem resistant; CT = computed tomography; CVVHDF = continuous venovenous hemodiafiltration; EA = Early Assessment; EOT = End of Treatment; GNB = Gram-negative bacteria; HAP = hospital-acquired pneumonia; ID = identification; INR = international normalized ratio; IV = intravenous; MIC = minimum inhibitory concentration; NA = not applicable; q12h = every 12 hours; RBC = red blood cell; SAE = serious adverse event; SGOT = serum glutamic oxaloacetic transaminase; SOFA = Sequential Organ Failure Assessment; TA = tracheal aspirate; TBL = total bilirubin; TOC = Test of Cure

**Study qualifying diagnosis:** Hospital-acquired pneumonia due to *A. baumannii* was identified with evidence of carbapenem resistance through treatment failure.

**Study qualifying infection history:** On Day -2, a sample obtained from the TA showed *A. baumannii* resistant to amikacin, ciprofloxacin, colistin, imipenem, and meropenem (Table 3). A sample obtained from the TA showed *K. pneumoniae* resistant to amikacin, aztreonam, cefepime, ceftolozane-tazobactam, ciprofloxacin, imipenem and meropenem. The culture was susceptible to ceftazidime-avibactam, colistin and tigecycline.

**Current hospitalization history:** The patient was hospitalized on Day -11 from an acute care treatment facility as an emergent admission onto the intensive care unit due to rupture of aorta aneurysm. The patient was placed on ventilation (continuous positive airway pressure [CPAP] + pressure support ventilation [PSV]) starting on Day -11 and continuing through Day 31. The onset date of infection was Day -2.

**Clinical course:** On Day -2, a microbiological laboratory sample was obtained from the TA, and WBC polymorphs (3+,  $\geq 25$ , many) and squamous epithelial cells (1+,  $< 10$ , few) were noted. Gram-negative rods (4+) were identified. The pathogen *A. baumannii* (quantitation,  $> 1.0 \times 10^5$ ) was identified.

On Day 1 (Screening/Baseline), a microbiological laboratory sample was obtained from the TA, and WBC polymorphs (3+,  $\geq 25$ , many) and squamous epithelial cells (1+,  $< 10$ , few) were noted. Gram-negative rods (4+) were identified. The pathogens *K. pneumoniae* (quantitation,  $> 1.0 \times 10^5$ ), *A. baumannii* (quantitation,  $> 1.00 \times 10^5$ ), and *E. coli* (quantitation,  $> 1.0 \times 10^5$ ) were identified. The chest radiograph showed right mid-lower lung field consolidation, increased density on all left lung fields; and no significant abnormality in the heart/vessels (Table 5). The patient was on T-piece without mechanical ventilation receiving supplemental oxygen; arterial blood gases (ABGs) indicated PaO<sub>2</sub> 100 mm Hg, PaCO<sub>2</sub> 25 mm Hg, SaO<sub>2</sub> 97%, and FiO<sub>2</sub> 45%. The initial clinical assessment of signs and symptoms revealed severe suctioned respiratory secretions, rales, rhonchi, and bronchial breath sounds. The SOFA score was 9, and the CPIS was 9 (Table 2). The inflammatory indices of WBC count, C-reactive protein (CRP), and body temperature were  $24.24 \times 10^9/L$ , 169 mg/dL, and 37.4°C, respectively (Table 1).

The patient received first dose of cefiderocol on Day 1 and received 26 subsequent doses from Days 2 to 14.

On Day 4 (EA), a microbiological laboratory sample was obtained from the TA, and WBC polymorphs (2+, 10 to 24, moderate) and squamous epithelial cells (1+,  $< 10$ , few) were noted. No pathogen was identified. The chest radiograph showed right mid-lower lung field consolidation, increased density on all left lung fields; and no change in comparison to lung fields at Screening. The patient was receiving supplemental oxygen via T-piece; ABGs indicated PaO<sub>2</sub> 124 mm Hg, PaCO<sub>2</sub> 26 mm Hg, SaO<sub>2</sub> 98%, and FiO<sub>2</sub> 35%. Signs and symptoms revealed moderate suctioned respiratory secretions, rales, rhonchi, and bronchial breath sounds. The SOFA score was 6, and the CPIS was 4. The inflammatory indices of WBC count, CRP, and body temperature were  $15.10 \times 10^9/L$ , 170 mg/dL, and 37.2°C, respectively. The patient was considered a clinical failure.

On Day 7, the patient experienced the SAE of lower gastrointestinal bleeding. The dose of study medication was not changed. The patient was recovering from the event. The investigator considered the event severe and not related to study medication. The SAE led to anemia and the patient received 2 units of packed RBCs. An endoscopy was planned for further assessment.

On Day 9, the patient experienced the SAE of descending colon, sigmoid colon, and rectum ischemia leading to perforation and peritonitis. Blood sample showed WBC 21980/ $\mu$ L (reference range [RR] 4000 to 11000), and procalcitonin 4.15 ng/mL (RR 0.1 to 0.5). The dose of study medication was not changed. Treatment included fresh frozen plasma. The dose of study medication was not changed. The investigator considered the event severe and not related to study medication. The SAE was diagnosed with a colonoscopy and bowel ischemia was noted. A CT scan showed perforation; a

laparotomy was performed with excision of the descending colon, sigmoid colon, and rectum. The SAE was considered a consequence of the abdominal aortic aneurysm rupture. The patient did not recover from the event.

On Day 12, the patient experienced the SAE of abnormal liver function test. The dose of study medication was not changed. The patient did not recover from the event. The investigator considered the event severe and not related to study medication. The TBL elevation was considered related to the septic profile of the patient. An ultrasound imaging along with laboratory assessments (viral hepatitis serology) were planned.

On Day 14 (EOT), a microbiological laboratory sample was collected from the TA, and WBC polymorphs (3+,  $\geq 25$ , many) and squamous epithelial cells (1+,  $< 10$ , few) were noted. Gram-negative rods (4+) were identified. The pathogens *A. baumannii* (quantitation,  $> 1.0 \times 10^5$ ), *P. aeruginosa* (quantitation,  $> 1.0 \times 10^5$ ), and *K. pneumoniae* (quantitation,  $1.0 \times 10^4$ ) were identified. Another microbiological sample was obtained from the blood. The pathogen *E. faecium* was identified. The chest radiograph showed diffuse opacity of all fields on the left lung and patchy infiltrates of the lower fields on the right lung, and no change in comparison of lung fields to Screening. The patient was receiving supplemental oxygen via T-piece; ABGs indicated PaO<sub>2</sub> 122 mm Hg, PaCO<sub>2</sub> 22 mm Hg, SaO<sub>2</sub> 99%, and FiO<sub>2</sub> 35%. Signs and symptoms revealed severe suctioned respiratory secretions, rales, rhonchi, and bronchial breath sounds. The SOFA score was 10, and the CPIS was 3. The inflammatory indices of WBC count, CRP, and body temperature were  $25.15 \times 10^9/L$ , 64.6 mg/dL, and 37.2°C, respectively. Clinical and microbiological outcomes showed clinical cure and persistence, respectively.

On Day 14, the patient experienced the SAE of *E. faecium* bacteremia. Treatment included daptomycin. The dose of study medication was not changed. The patient recovered from the event. The investigator considered the event severe and not related to study medication.

On Day 16, the AE of thrombocytopenia (moderate) was reported. The low platelet count was attributed to the septic episode that followed colon ischemia, perforation, and peritonitis. The outcome of the event was not recovered/not resolved and causality was reported as not related to study drug. Sultamicillin was started on Day 18 for 7 days for treatment of pneumonia.

On Day 19, a microbiological laboratory sample was collected from the pleural fluid, and WBC polymorphs (3+,  $\geq 25$ , many) were noted. Gram-negative rods (4+) were identified. The pathogens *K. pneumoniae* (no quantitation) and *P. aeruginosa* (no quantitation) were identified. The patient experienced the SAE of empyema. Pleural fluid results showed: pH 7.11 (RR  $> 7.20$ ); pleural fluid glucose 2 (RR  $> 0.5$  of serum glucose); pleural fluid cells 50000/mm<sup>3</sup> (RR 0). Treatment included levofloxacin, ceftazidime-avibactam, colistimethate sodium, colistin, and amikacin. The patient did not recover from the event. The investigator considered the event severe and not related to study medication.

On Day 23, the TOC assessment was completed. Two microbiological laboratory samples were collected from the TA and WBC polymorphs (2+, 10 to 24, moderate) and

squamous epithelial cells (1+, < 10, few) were noted. In one sample, Gram-negative rods (3+) were identified and the pathogen *K. pneumoniae* (quantitation,  $< 1 \times 10^3$ ) was identified. In the second sample, Gram-negative rods (5+) were identified and the pathogen *P. aeruginosa* (quantitation,  $> 1 \times 10^5$ ) was identified. The chest radiograph showed diffuse infiltrations of all pulmonary fields on both lungs, and the lung fields were considered worsened in comparison to Screening. The patient was receiving supplemental oxygen via T-piece; ABGs indicated PaO<sub>2</sub> 102 mm Hg, PaCO<sub>2</sub> 24 mm Hg, SaO<sub>2</sub> 97%, and FiO<sub>2</sub> 40%. Signs and symptoms revealed severe suctioned respiratory secretions, rales, rhonchi, and bronchial breath sounds. The SOFA score was 16, and the CPIS was 3. The patient was slightly hypotensive (90/50 mm Hg), and clinical signs and symptoms included severe suctioned respiratory secretions, rales, rhonchi, and bronchial breath sounds.

Blood sample results showed a very high WBC count with raised neutrophils, high partial thromboplastin time (PTT), alkaline phosphatase (ALP), alanine aminotransferase (ALT); aspartate aminotransferase (AST), gamma glutamyl transferase (GGT), lactate dehydrogenase (LDH), amylase, and TBL. The inflammatory indices of WBC count, CRP, and body temperature were  $36.13 \times 10^9$ /L, 110.0 mg/dL, and 37.4°C, respectively. The outcomes were assessed as clinical failure with microbiological persistence.

On Day 25, the Follow-up visit was completed. Three microbiological laboratory samples were collected from the TA and WBC polymorphs (1+, < 10, few) and squamous epithelial cells (1+, < 10, few) were noted. In one sample, Gram-negative rods (5+) were identified and the pathogen *K. pneumoniae* (quantitation,  $1 \times 10^4$ ) was identified. In the second sample, Gram-negative rods (4+) were identified and the pathogen *P. aeruginosa* (quantitation,  $1 \times 10^5$ ) was identified. In the third sample, Gram-negative rods (4+) were identified, and the pathogen *S. maltophilia* (quantitation,  $1 \times 10^4$ ) was identified. The chest radiograph showed diffuse infiltrates on both lungs, predominantly in lower lung fields, the presence of 2 chest tubes on right lung, and subcutaneous emphysema; and the lung fields were considered worsened in comparison to Screening. The patient was receiving supplemental oxygen via T-piece; ABGs indicated PaO<sub>2</sub> 78 mm Hg, PaCO<sub>2</sub> 26 mm Hg, SaO<sub>2</sub> 96%, and FiO<sub>2</sub> 40%. Clinical signs and symptoms included severe suctioned respiratory secretions, rales, rhonchi, and bronchial breath sounds. The SOFA was 17 and the CPIS was 7. Blood sample results showed a very high WBC count with raised neutrophils, high PTT, ALP, ALT, AST, GGT, LDH (2774 U/L), creatine phosphokinase, and TBL. The inflammatory indices of WBC count, CRP, and body temperature were  $27.94 \times 10^9$ /L, 128 mg/dL, and 37.5°C, respectively. The patient was considered a clinical failure with microbiological persistence.

On Day 29, the patient experienced the SAE of septic shock. Treatment included levofloxacin and meropenem. The outcome was Fatal. The investigator considered the event severe and not related to study medication.

On Day 31, the patient completed the study and died due to multiple organ failure and the SAE of septic shock, 17 days after receiving his last dose of study medication. The investigator considered the event not related to the study medication.

**Table 1 Inflammatory Indices**

Visit	White Blood Cell Count (RR = 4.2 to 10.8)	C-reactive Protein (RR = NA)	Body Temperature
Screening/Baseline	$24.24 \times 10^9/L$	169 mg/L	37.4°C
Early Assessment	$15.10 \times 10^9/L$	170 mg/L	37.2°C
End of Treatment	$25.15 \times 10^9/L$	64.6 mg/L	37.2°C
Test of Cure	$36.13 \times 10^9/L$	110.0 mg/L	37.4°C
Follow-up	$27.94 \times 10^9/L$	128 mg/L	37.5°C

NA = not available; RR = reference range

**Table 2 Sequential Organ Failure Assessment and Total Clinical Pulmonary Infection Score Status**

Visit	SOFA Score	Total CPIS
Screening/Baseline	9	9
Early Assessment	6	4
End of Treatment	10	3
Test of Cure	16	3
Follow-up	17	7

CPIS = Clinical Pulmonary Infection Score; SOFA = Sequential Organ Failure Assessment

**Table 3 Antimicrobial Susceptibility Testing at Screening (European Committee on Antimicrobial Susceptibility Testing)**

Pathogen	Resistant	Intermediate	Susceptible	Not Applicable
<i>Acinetobacter baumannii</i>	Amikacin, ciprofloxacin, colistin, imipenem, and meropenem	NA	NA	Aztreonam, ceftazidime-tazobactam, ceftolozane-avibactam, cefiderocol, tigecycline, cefepime
<i>Klebsiella pneumoniae</i>	Amikacin, aztreonam, cefepime, ceftolozane-tazobactam, ciprofloxacin, imipenem, meropenem	NA	Ceftazidime-avibactam, colistin, tigecycline	Cefiderocol

NA = not applicable

**Table 4 Susceptibility Testing at Each Visit**

Visit	IHMA Organism ID	AMK	AZT	CFPM	CAZ/ AVI	CEF/ TAZ	CPFX	CST	IPM	MEPM	CFDC	TGC
		MIC µg/mL										
Screening/ Baseline	<i>Acinetobacter baumannii</i> Sample ID E859222	> 64	> 32	> 16	64	32	> 4	> 8	64	> 64	0.5	2
Screening/ Baseline	<i>Klebsiella pneumoniae</i> Sample ID E859214	32	> 32	16	1	32	1	2	32	16	0.25	0.5
EOT	<i>Klebsiella pneumoniae</i> Sample ID E859217	16	> 32	> 16	1	32	4	2	64	64	2	1
EOT	<i>Acinetobacter baumannii</i> Sample ID E859218	> 64	> 32	> 16	32	16	> 4	4	64	64	0.25	2
EOT	<i>Pseudomonas aeruginosa</i> Sample ID E859219	≤ 4	16	2	2	0.25	≤ 0.25	1	2	0.06	0.25	4
TOC	<i>Pseudomonas aeruginosa</i> Sample ID E859216	≤ 4	32	8	4	0.5	≤ 0.25	1	2	0.25	0.5	> 4
TOC	<i>Klebsiella pneumoniae</i> Sample ID E859220	32	> 32	> 16	1	32	> 4	2	32	64	2	2

Visit	IHMA Organism ID	AMK	AZT	CFPM	CAZ/ AVI	CEF/ TAZ	CPFX	CST	IPM	MEPM	CFDC	TGC
		MIC µg/mL										
FU	<i>Pseudomonas aeruginosa</i> Sample ID E859221	≤ 4	16	4	8	0.5	≤ 0.25	1	1	0.25	0.25	4
FU	<i>Klebsiella pneumoniae</i> Sample ID E876275	16	> 32	> 16	1	32	2	1	32	64	1	0.5

AMK = amikacin; AZT = aztreonam; CAZ/AVI = ceftazidime-avibactam; CEF/TAZ = ceftolozane-tazobactam; CFDC = cefiderocol; CFPM = cefepime; CPFX = ciprofloxacin; CST = colistin; ID = identification; IHMA = International Health Management Associates; IPM = imipenem; MEPM = meropenem; MIC = minimum inhibitory concentration; TGC = tigecycline

**Table 5 Chest Radiograph Results**

Visit	Lung Fields/ Airways	Heart/ Vessels	Other Structures	Comparison of Lung Fields to Screening
Screening/Baseline	Right mid-lower lung field consolidation, increased density on all left lung fields	No significant abnormality	NA	NA
Early Assessment	Right mid-lower lung field consolidation, increased density on all left lung fields	NA	NA	No change
End of Treatment	Diffuse opacity of all fields on the left lung and patchy infiltrates of the lower fields on the right lung.	No abnormal findings	No abnormal findings	No change
Test of Cure	Diffuse infiltrations of all pulmonary fields on both lungs	No abnormal findings	No abnormal findings	Worsened
Follow-up	Diffuse infiltrates on both lungs, predominantly in lower lung fields. Presence of 2 chest tubes on right lung. Subcutaneous emphysema	No abnormal findings	No abnormal findings	Worsened

NA = not applicable

**Table 6 Liver Function Tests**

Visit	AST (RR = 10 to 40)	ALT (RR = 10 to 40)	ALP (RR = 25 to 125)	GGT (RR = 10 to 49)	Total Bilirubin (RR = 0.3 to 1.2)
Screening/Baseline	32 IU/L	68 IU/L	215 U/L	132 IU/L	3.5 mg/dL
Early Assessment	38 IU/L	78 IU/L	228 U/L	116 IU/L	3.3 mg/dL
End of Treatment	113 IU/L	87 IU/L	480 U/L	181 IU/L	12.4 mg/dL
Test of Cure	238 IU/L	146 IU/L	407 U/L	371 IU/L	24.6 mg/dL
Follow-up	1573 IU/L	628 IU/L	434 U/L	194 IU/L	18.3 mg/dL

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase;  
GGT = gamma-glutamyl transferase; RR = reference range

**Table 7 Renal Function Tests**

Visit	Blood Urea Nitrogen (RR = 10 to 50)	Serum Creatinine (RR = 0.8 to 1.3)	Creatinine Clearance
Screening/Baseline	50 mg/dL	2.2 mg/dL	32.88 mL/min
Early Assessment	19 mg/dL	0.9 mg/dL	80.37 mL/min
End of Treatment	40 mg/dL	0.8 mg/dL	90.42 mL/min
Test of Cure	19 mg/dL	0.5 mg/dL	144.67 mL/min
Follow-up	14 mg/dL	0.6 mg/dL	120.56 mL/min

RR = reference range

**Table 8 Coagulation Tests**

Visit	Platelet Count (RR = 140 to 350)	aPTT (RR = 24 to 35)	PT-INR (RR = 0.9 to 1.1)
Screening/Baseline	$668 \times 10^9/L$	41.2 sec	1.38
Early Assessment	$568 \times 10^9/L$	33.3 sec	1.20
End of Treatment	$69 \times 10^9/L$	48.6 sec	1.38
Test of Cure	$97 \times 10^9/L$	47.2 sec	1.67
Follow-up	$50 \times 10^9/L$	61.4 sec	1.93

aPTT = activated partial thromboplastin time; PT-INR = prothrombin international normalized ratio;  
RR = reference range

## Subject ID Patient # 19

Subject ID	Patient # 19	Country	Greece			
Age	64	Clinical Diagnosis at Screening	BSI Primary BSI due to XDR <i>Acinetobacter baumannii</i>			
Gender	Female	Severity	Moderate			
Race	White	APACHE II Score	13			
Height (cm)	160.0	Causative Pathogen at Screening	<i>A. baumannii</i>			
Body Weight (kg)	70.0	CR Evidence at Screening (other than central lab)	Positive rapid diagnostic test			
MIC of Meropenem	64 µg/mL	MIC of Cefiderocol	0.12 µg/mL			
MIC of Imipenem	> 64 µg/mL					
Duration of Study Treatment	9 days	Standard of Care	Tigecycline (100 mg IV), colistimethate sodium (4500000 IU IV), daptomycin (350 mg IV)			
Study Drug	Cefiderocol 1.5 g and 2 g q8h IV					
Microbiological Results at TOC		Day 28 All-cause Mortality		Clinical Outcome at TOC		
Indeterminate		Death (Day 11)		NA		
Medical History (Ongoing)	Bronchial asthma; glaucoma; chronic obstructive pulmonary disease; hypertension; chronic respiratory failure; possible penicillin allergy (the patient has been evaluated by allergist/immunologist who considered her eligible for cephalosporins); VAT (due to <i>A. baumannii</i> ), allergic bronchopulmonary aspergillosis					
Medical History (Not Ongoing)	Peptic ulcer (duodenal ulcer), right shoulder fracture surgical treatment (after road accident); breast cancer of the left breast, treated with breast conserving surgery and radiation therapy; lower respiratory tract infection					
Adverse Event	Day	Severity	Action Taken with Study Drug	Outcome	Causality	Serious
Septic shock	8	Severe	Drug withdrawn	Fatal	Not related	Yes
Narrative Summary						
<p>A 64-year-old female patient from Greece had a medical history of bronchial asthma, COPD, hypertension, breast cancer of left breast (treated with breast conserving surgery/radiation therapy), and chronic respiratory failure.</p> <p>The patient was admitted to the hospital from home on Day -18 with symptoms of acute COPD exacerbation and a lower respiratory tract infection. Acute exacerbation of COPD was treated with inhaled SABAs, SAMAs, and corticosteroids including methylprednisolone (ICS and systemic), whereas the lower respiratory tract infection was treated with empiric antimicrobial therapy consisting of ceftaroline from Days -14 to -9 and IV ciprofloxacin from Days -18 to -15. The patient underwent a bronchoscopy and received cisatracurium on Day -11. Oseltamivir was given from Days -16 to -10. Despite treatment, the patient was intubated on Day -15 due to hypercapnic respiratory failure after failing a noninvasive ventilation trial. Linezolid was provided on Day -15, and on the same day, the patient was transferred to the ICU and norepinephrine was started for hypotension and remained in place until Day 11; work-up revealed RSV infection. She was attached to mechanical ventilation on Day -15 and remained attached throughout hospitalization. She received ceftriaxone and moxifloxacin on Day -14 and azithromycin from Day s-14 to -11. On Day -8, allergic bronchopulmonary aspergillosis was reported. It was reported that during ICU stay, the patient developed VAT due to <i>A. baumannii</i> on Day -8. On Days -9 to -7, piperacillin-tazobactam was given, and colistin was provided through respiratory inhalation on Days -7 to Dav -2 and IV on Dav -7 to Day 1 for the VAT. Gentamicin was administered on Dav -1, with tigecycline</p>						

and daptomycin provided on the next day. On Day -7, *A. baumannii* was isolated from endotracheal aspirates. Despite treatment with colistin, the patient developed fever and leukocytosis. On Day -2, XDR *A. baumannii* was isolated from blood cultures. Susceptibility testing showed resistance to colistin and carbapenems with moderate susceptibility to tigecycline.

On Day 1, the patient was screened for study eligibility and enrolled with a clinical diagnosis of BSI (primary BSI due to XDR *A. baumannii*). The rapid diagnostic test was positive (direct blood specimen, chromogenic media) for evidence of carbapenem-resistant, Gram-negative bacilli. The TA and urine (from indwelling catheter) cultures collected on this date were negative. The patient was randomized to cefiderocol on Day 1. Cefiderocol was provided from Days 1 to Day 9. On Day 4, mechanical ventilation was attempted to be weaned for discontinuation. On Day 4 (EA), the clinical outcome was assessed as clinical failure.

On Day 7, the patient developed hemodynamic deterioration with an increased lactate and worsening of renal function. Clinical examination revealed abdominal tenderness. An abdominal CT performed showed mild edema of the rectum-sigmoid colon. On Day 8, the patient experienced the unrelated SAE of septic shock. Vancomycin was provided with metronidazole, hydrocortisone, and human albumin. WBC count was high at 28470/mm<sup>3</sup> (RR < 11000/mm<sup>3</sup>) and procalcitonin was 1.27 ng/mL (RR < 0.5 ng/mL). The patient was re-intubated, and mechanical ventilation was initiated. Empiric treatment for *Clostridium difficile* and Gram-positives was initiated. CVVHDF was started on Day 8 and continued.

On Day 9 (EOT), the study drug regimen was withdrawn due to the SAE of septic shock. Clinical signs and symptoms included severe hemodynamic instability and moderate abdominal tenderness with deep palpation. Blood cultures remained negative. Clinical outcome was assessed as clinical failure with indeterminate microbiological outcome. The patient remained in shock with hemodynamic characteristics highly suggestive of distributive shock. CRRT was initiated due to oliguria and metabolic acidosis. Colistin, gentamicin, and ceftazidime/avibactam were initiated for the SAE of septic shock. Anidulafungin is started empirically as antifungal prophylaxis. Additional blood sample results showed a high aPTT at 107.3 seconds and a high creatine kinase at 1077 U/L. The patient remained on CRRT. On Day 11, the patient remained in critical condition requiring large amounts of vasopressors. His lactic acidosis worsened and chest x-ray showed a new right lower lung field opacity. Cardiac ultrasound showed preserved systolic function. The patient died on Day 11. Reasons of death cited in the death certificate were septic shock, multi-organ failure, chronic obstructive pulmonary disease, and chronic respiratory failure. TA cultures (collected Day 11) showed pan-drug resistant *A. baumannii*. The isolate was reported to be resistant to cefiderocol. Catheter tip cultures (site not specified) were negative, and *C. difficile* testing was negative (antigen and toxin A and B). The investigator reported causality to be not related to study drug.

APACHE = Acute Physiology and Chronic Health Evaluation; aPTT = activated partial thromboplastin time; BSI = blood stream infection; COPD = chronic obstructive pulmonary disease; CPK = creatine phosphokinase; CR = carbapenem resistance; CRRT = continuous renal replacement therapy; CT = computed tomography; EA = Early Assessment; EOT = End of Treatment; ICS = inhaled corticosteroids; ICU = intensive care unit; ID = identification; IV = intravenous; MIC = minimum inhibitory concentration; NA = not available; RR = reference range; RSV = respiratory syncytial virus; SABAs = short-acting inhaled beta-agonists; SAE = serious adverse event; SAMAs = short-acting muscarinic-antagonists; TA = tracheal aspirate; TOC = Test of Cure; unk = unknown; VAT = ventilator-associated tracheobronchitis; WBC = white blood cell; XDR = extensively drug resistant

**Study qualifying diagnosis:** Primary BSI due to *A. baumannii* was identified with a positive rapid diagnostic test (chromogenic media).

**Study qualifying infection history:** On Day -2, a sample obtained from the blood showed *A. baumannii* resistant to amikacin, ciprofloxacin, colistin, imipenem, and meropenem (Table 3).

**Current hospitalization history:** The patient was hospitalized on Day -18 from home as an emergency admission onto a general ward due to lower respiratory tract infection and chronic obstructive pulmonary disease. The patient was placed on a ventilator, CMV (continuous mandatory ventilation) starting on Day -15 to Day -11. The patient was placed on continuous positive airway pressure (CPAP) and pressure support ventilation (PSV) on Day -11 to Day -3, CMV on Day -3 to Day -2, CPAP and PSV on Day -2 to Day 3, and CMV on Day 8 to Day 11. The onset date of BSI was Day -2.

**Clinical course:** On Day -2, a microbiological laboratory sample was obtained from the blood. The pathogen *A. baumannii* was identified.

On Day 1 (Screening/Baseline), microbiological laboratory samples were obtained from the blood and urine (indwelling catheter); both cultures were negative. A microbiological laboratory sample was obtained from the TA, and WBC polymorphs (3+,  $\geq 25$ , many) were noted. The culture result was negative. The patient was on a ventilator; arterial blood gases (ABGs) indicated PaO<sub>2</sub> 76 mm Hg, PaCO<sub>2</sub> 33 mm Hg, SaO<sub>2</sub> 96 %, and FiO<sub>2</sub> 25%. The initial clinical assessment of signs and symptoms revealed mild signs and symptoms of causative infection (no further information reported). The Sequential Organ Failure Assessment (SOFA) score was 3 (Table 2). The inflammatory indices of WBC count, C-reactive protein (CRP), and body temperature were  $19.58 \times 10^9/L$ , 4.98 mg/dL, and 37.6°C, respectively (Table 1).

The patient received her first dose of cefiderocol (2 g q8h IV) on Day 1, and she received 16 subsequent doses on Day 2 through Day 7. The patient received 6 subsequent doses of cefiderocol (1.5 g q8h IV) on Day 7 to Day 9. Tigecycline was provided on Day 1 as an adjunctive antibiotic. The patient was also administered daptomycin on Day 1.

On Day 4 (EA), a microbiological laboratory sample was obtained from the blood. The culture was negative. The ABGs indicated PaO<sub>2</sub> 125 mm Hg, PaCO<sub>2</sub> 28 mm Hg, SaO<sub>2</sub> 99%, and FiO<sub>2</sub> 32%. The signs and symptoms of the causative infection were absent. The SOFA score was 4. The inflammatory indices of WBC count, CRP, and body temperature were  $17.23 \times 10^9/L$ , 1.77 mg/dL, and 37.6°C, respectively. The clinical outcome was assessed as a clinical failure.

On Day 7, the patient developed hemodynamic deterioration and worsening of renal function. Clinical examination revealed abdominal tenderness. An abdominal computed tomography scan performed showed mild edema of rectum-sigmoid colon, with no other specific findings.

On Day 8, the patient experienced the SAE of septic shock. Procalcitonin was 1.27 ng/mL (RR < 0.5 ng/mL). The investigator considered the event severe. The patient was re-intubated, and mechanical ventilation was initiated. Empiric treatment for septic shock was initiated including vancomycin on Day 8 to Day 11, metronidazole on Day 8 to Day 11, gentamicin on Day 9, avibactam/ceftazidime on Day 9 to Day 11, and colistin on Day 9 to Day 11.

On Day 9 (EOT), a microbiological laboratory sample was obtained from the blood. The culture was negative. The patient was on a ventilator; ABGs indicated PaO<sub>2</sub> 83 mm Hg, PaCO<sub>2</sub> 31 mm Hg, SaO<sub>2</sub> 97%, and FiO<sub>2</sub> 30%. Clinical signs and symptoms included severe hemodynamic instability and moderate abdominal tenderness on deep palpation. The SOFA score was 7. The inflammatory indices of WBC count, CRP, and body temperature were  $19.49 \times 10^9/\text{L}$ , 2.87 mg/dL, and 36.6°C, respectively. The study drug regimen was withdrawn on Day 9 due to the SAE of septic shock. The clinical outcome was assessed as clinical failure with indeterminate microbiological outcome. On Day 11, a microbiological laboratory sample was obtained from the TA, and WBC polymorphs (3+,  $\geq 25$ , many) were noted. Gram-negative rods (+) were identified. The pathogen *A. baumannii* (quantitation,  $1 \times 10^4$ ) was identified. The patient remained in shock with hemodynamic characteristics highly suggestive of distributive shock. Continuous renal replacement therapy was initiated due to oliguria and metabolic acidosis. Colistin, gentamicin, and ceftazidime/avibactam were initiated for the SAE of septic shock. Anidulafungin was started empirically as antifungal prophylaxis. Additional blood sample results showed high activated partial thromboplastin time at 107.3 seconds and high creatine kinase at 1077 U/L. The SAE of septic shock was Fatal, and the patient died on Day 11, 3 days after receiving her last dose of study medication.

**Table 1 Inflammatory Indices**

Visit	White Blood Cell Count (RR = 4.6 to 10.2)	C-reactive Protein (RR = 0 to 0.29)	Body Temperature
Screening/Baseline	$19.58 \times 10^9/\text{L}$	4.98 mg/dL	37.6°C
Early Assessment	$17.23 \times 10^9/\text{L}$	1.77 mg/dL	37.6°C
End of Treatment	$19.49 \times 10^9/\text{L}$	2.87 mg/dL	36.6°C

RR = reference range

**Table 2 Sequential Organ Failure Assessment Score Status**

Visit	SOFA Score
Screening/Baseline	3
Early Assessment	4
End of Treatment	7

SOFA = Sequential Organ Failure Assessment

**Table 3 Antimicrobial Susceptibility Testing at Screening (European Committee on Antimicrobial Susceptibility Testing)**

Pathogen	Resistant	Intermediate	Susceptible	Not Applicable
<i>Acinetobacter baumannii</i>	Amikacin, ciprofloxacin, colistin, imipenem, meropenem	NA	NA	Aztreonam, ceftazidime-avibactam, ceftolozane-tazobactam, cefiderocol, tigecycline, cefepime

NA = not applicable

**Table 4 Susceptibility Testing at Each Visit**

Visit	IHMA Organism ID	AMK	AZT	CFPM	CAZ/ AVI	CEF/ TAZ	CPFX	CST	IPM	MEPM	CFDC	TGC
		MIC µg/mL										
Screening/ Baseline	<i>Acinetobacter baumannii</i> E844981	> 64	> 32	> 16	64	16	> 4	> 8	> 64	64	0.12	2

AMK = amikacin; AZT = aztreonam; CFDC = cefiderocol; CPFX = ciprofloxacin; CAZ/AVI = ceftazidime-avibactam; CST = colistin;  
CEF/TAZ = ceftolozane-tazobactam; CFPM = cefepime; ID = identification; IHMA = International Health Management Associates; IPM = imipenem;  
MEPM = meropenem; MIC = minimum inhibitory concentration; TGC = tigecycline

**Table 5 Liver Function Tests**

Visit	AST (RR = 10 to 31)	ALT (RR = 10 to 31)	ALP (RR = 34 to 120)	GGT (RR = 9 to 35)	Total Bilirubin (RR = 0.2 to 1.2)
Screening/Baseline	27 U/L	116 U/L	70 U/L	214 U/L	0.4 mg/dL
Early Assessment	26 U/L	85 U/L	64 U/L	224 U/L	0.7 mg/dL
End of Treatment	128 U/L	120 U/L	427 U/L	118 U/L	0.4 mg/dL

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase;  
GGT = gamma-glutamyl transferase; RR = reference range

**Table 6 Renal Function Tests**

Visit	Blood Urea Nitrogen (RR = 10 to 50)	Serum Creatinine (RR = 0.6 to 1.2)	Creatinine Clearance
Screening/Baseline	38.27 mg/dL	0.6 mg/dL	104.67 mL/min
Early Assessment	50.4 mg/dL	0.8 mg/dL	78.50 mL/min
End of Treatment	26.13 mg/dL	0.6 mg/dL	104.67 mL/min

RR = reference range

**Table 7 Coagulation Tests**

Visit	Platelet Count (RR = 140 to 450)	aPTT (RR = 28 to 40)	PT-INR (RR = 0.9 to 1.1)
Screening/Baseline	$285.7 \times 10^9/L$	30.2 sec	1.05
Early Assessment	$381.2 \times 10^9/L$	31.8 sec	1.39
End of Treatment	$201.7 \times 10^9/L$	107.3 sec	1.41

aPTT = activated partial thromboplastin time; PT-INR = prothrombin international normalized ratio;  
RR = reference range

## Subject ID Patient # 20

Subject ID	Patient # 20	Country	France			
Age	68	Clinical Diagnosis at Screening	Sepsis (initially)/ HAP (final)			
Gender	Male	Severity	Severe			
Race	Other	APACHE II Score	18			
Height (cm)	172.0	Causative Pathogen at Screening	Enterobacter cloacae			
Body Weight (kg)	67.8	CR Evidence at Screening (other than central lab)	Hospital antibiogram			
MIC of Meropenem	64 µg/mL	MIC of Cefiderocol	16 µg/mL			
MIC of Imipenem	32 µg/mL					
Duration of Study Treatment	6 days	Standard of Care	Amikacin 1000 mg IV Fosfomycin (4 g q12h IV)			
Study Drug		Cefiderocol (2/1.5 g q8h IV)				
Microbiological Results at TOC		Day 28 All-cause Mortality		Clinical Outcome at TOC		
Indeterminate		Death (Day 12)		Clinical failure		
Medical History (Ongoing)	Adjustment disorder, aspirin allergy, benign prostatic hyperplasia, dysphagia, hyperlactemia, milk products intolerance, protein energetic malnutrition, smoking, strictures of esophagus, veinous stripping, dyspnea on exertion, pulmonary emphysema, anxiety-depressive syndrome, hypertension, atrial fibrillation, hypertrophic cardiomyopathy, chronic kidney disease; adenocarcinoma of lower right esophagus with metastatic invasion with 13 of 14 lymph nodes positive; carbapenemase producing Enterobacteriaceae portage; infectious syndrome; right spontaneous pneumothorax					
Medical History (Not Ongoing)	Alcoholism; gastrostomy; esophagectomy					
Adverse Event	Day	Severity	Action Taken with Study Drug	Outcome	Causality	Serious
Asthenia	3	Severe	Dose not changed	Not recovered/ not resolved	Not related	No
Deterioration of respiratory functions during the night between Days 2 and 3	3	Moderate	Dose not changed	Recovered/ resolved	Not related	Yes
Consciousness disorders	3	Moderate	Dose not changed	Recovered/ resolved	Not related	No
Hepatic cytolys on Day 5 not medically relevant with AST > 5 x ULN	5	Moderate	Dose not changed	Recovered/ resolved	Not related	No

Gastrointestinal haemorrhage	11	Severe	Not applicable	Not recovered/ not resolved	Not related	Yes
Neurological failure	11	Severe	Not applicable	Not recovered/ not resolved	Not related	Yes
Fever	11	Severe	Not applicable	Recovered/ resolved	Not related	No
Bilateral lung congestion	11	Mild	Not applicable	Not recovered/ not resolved	Not related	No
Hyperkalemia	11	Moderate	Not applicable	Recovered/ resolved	Not related	No
Deterioration of respiratory function	12	Severe	Not applicable	Fatal	Not related	Yes

#### Narrative Summary

A 68-year-old white male from France had a history of adenocarcinoma of lower right esophagus with metastatic invasion with 13 of 14 lymph nodes positive; carbapenemase producing *Enterobacteriaceae* portage; infectious syndrome; and alcoholism, smoking, protein energetic malnutrition, dyspnea on exertion, pulmonary emphysema, anxiety-depressive syndrome, hypertension, atrial fibrillation, hypertrophic cardiomyopathy, and chronic kidney disease on unknown dates.

On Day -5, the patient was hospitalized from home for elective esophagectomy and admitted to the ICU on Day -4 (on isolation). It was reported that on Day -3, the patient had a fever post-operatively with digestive colonization with resistant *Enterobacteria* (ongoing since Day -113). The patient was diagnosed with HAP on Day -2. On the same date, Day -2, the patient experienced a right spontaneous pneumothorax. Amiodarone chlorhydrate was provided on this date.

On Day -2, BAL fluid was collected and showed *E. cloacae* (results on Day 1).

On Day -1, the patient had a body temperature of 38.4°C with a respiratory rate of 26 breaths per minute. On Day -1, Screening/Baseline, clinical assessment showed the patient had severe fatigue with mild malaise. Other signs and symptoms included severe dyspnea, expectoration production, bronchial secretion aspiration, wheezing and gasping due to the lung infection; moderate hissing, gasp, rhonchi, and egophonia; and mild "platit" to percussion and cough. Chest x-ray showed tracheal deviation to the right, bilateral opacities, infiltrates predominant on the left side, and subcutaneous emphysema on the right side. Blood test results showed raised WBC count, AST, BUN, and creatinine. The patient was treated with caspofungin from Days -2 to 5.

On Day 1, the patient was enrolled based on a diagnosis of sepsis, which was later corrected to HAP. The patient was randomized to cefiderocol (1.5 g q8h IV) and received the first dose on Day 1.

On the same day, at 08:00 hours, the patient had a pulse rate at 157 bpm, respiratory rate at 20 breaths per minute, and body temperature at 38.0°C. The patient's condition deteriorated during the night between Days 2 and 3, which included deterioration of respiratory functions with a change in the level of consciousness (consciousness disorders).

On Day 3 (EA), at 16:00 hours, the patient's pulse rate was at 146 bpm, respiratory rate at 31 breaths per minute, and body temperature at 39.2°C. On the same day, the unrelated SAE of deterioration of respiratory functions during the night between Days 2 and 3, and the unrelated AE of consciousness disorders were reported. The patient was reintubated and the SAE recovered/resolved. On Day 4, at 08:00 hours, the patient's pulse rate was at 148 bpm with respiratory rate at 33 breaths per minute. At

around 20:00 hours, the patient's pulse rate was at 83 bpm with respiratory rate at 30 breaths per minute.

Pleural fluid cultures (collected Day -2) showed *E. cloacae* (no quantitation, heavy growth) on Day 5.

On Day 6, cefiderocol was discontinued. The site confirmed that study discs were utilized and the inhibition diameter was measured as = 0 mm. No microbiological samples were collected.

On Day 7, the pleural fluid drain culture (collected Day -2) showed *E. cloacae* (no quantitation, moderate growth) and the patient was treated with amoxicillin-clavulanic acid.

On Day 11, the unrelated SAE of gastrointestinal haemorrhage was reported as the patient had "old blood externalized by mouth and melena." The unrelated SAE of neurological failure was also reported; he experienced "agitation and confusion." Propofol was provided as sedation for the comfort of the patient. Additional unrelated AEs of fever, hyperkalemia, and bilateral lung congestion were all reported. The right chest drain was removed on Day 11.

The physician had discussions with the family and the decision was made to stop active treatments.

The patient was reported to have died on Day 12 (EOS) due to the SAE of deterioration of respiratory function. The SAEs of gastrointestinal haemorrhage and neurological failure were ongoing at the time of death. The investigator considered the 3 SAEs unrelated to study medication.

AE = adverse event; APACHE = Acute Physiology and Chronic Health Evaluation; AST = aspartate aminotransferase; BAL = bronchoalveolar lavage; bpm = beats per minute; BUN = blood urea nitrogen; CPK = creatine phosphokinase; CR = carbapenem resistance; EA = Early Assessment; EOS = End of Study; EOT = End of Treatment; HAP = hospital-acquired pneumonia; ICU = intensive care unit; IV = intravenous; MIC = minimum inhibitory concentration; PT-INR = prothrombin international normalized; q8h = every 8 hours; q12h = every 12 hours; SAE = serious adverse event; TOC = Test of Cure; ULN = upper limit of normal; unk = unknown; WBC = white blood cell

**Study qualifying diagnosis:** Sepsis initially followed by HAP due to *E. cloacae* identified to be CR through a hospital antibiogram.

**Study qualifying infection history:** On Day -2, *E. cloacae* resistant to aztreonam, cefepime, ceftazidime-avibactam, ceftolozane-tazobactam, ciprofloxacin, imipenem, and meropenem was identified from the BAL fluid. The isolate was susceptible to amikacin, colistin, and tigecycline (Table 3).

**Current hospitalization history:** The patient was hospitalized on Day -5 due to a scheduled esophagectomy on Day -4 as an elective admission and placed into isolation and was subsequently transferred into the ICU on Day -4.

The patient was placed on ventilation from Day -2 to Day -1 (continuous mandatory ventilation [CMV]), followed by pressure support ventilation (PSV) from Day -1 to Day 2, CMV on Day 3, PSV on Day 6, and CMV from Days 6 to 9.

**Clinical course:** On Day -2, a microbiological laboratory sample was collected from the pleural fluid drain. The pathogen *E. cloacae* (no quantitation, moderate growth) was identified. Another microbiological laboratory sample was obtained from the BAL fluid, and WBC polymorphs (3+,  $\geq 25$ , many) and squamous epithelial cells (1+,  $< 10$ , few) were noted. Gram-negative rods (3+) were identified. The pathogen *E. cloacae* (quantitation,  $1.0 \times 10^5$ ) was identified. A third microbiological laboratory sample was collected from the pleural fluid, and WBC polymorphs (3+,  $\geq 25$ , many) were noted. The pathogens *K. pneumoniae* (quantitation,  $1.0 \times 10^5$ ) and *E. cloacae* (no quantitation, heavy

growth) were identified. The patient was on a ventilator; pulse oximetry on Day -1 showed SpO<sub>2</sub> was 96% and FiO<sub>2</sub> was 55%. The initial assessment of signs and symptoms noted severe fatigue with mild malaise. Other signs and symptoms included severe dyspnea, expectoration production, bronchial secretion aspiration, wheezing and gasping due to the lung infection; moderate hissing, gasp, rhonchi, and egophonia; and mild “platit” to percussion and cough. Chest x-ray was reported to have tracheal deviation to the right, bilateral opacities and infiltrates predominant on the left side, and subcutaneous emphysema on the right side, endotracheal tube, nasogastric tube and surgical staple (Table 5). The Sequential Organ Failure Assessment (SOFA) score was 8 (Table 2). The inflammatory indices of WBC count and body temperature were  $24.1 \times 10^9/\text{L}$  and 38.4°C, respectively (Table 1). Blood test results revealed a PT-INR at 1.6 (reference range [RR] 0.0 to 1.2), AST at 56 IU/L (RR 15 to 37), BUN at 36.96 mmol/L (RR 2.5 to 6.4), and creatinine at 136 µmol/L (RR 59.2 to 104).

The patient received his first infusion of cefiderocol 1.5 g q8h IV on Day 1. The patient received 5 subsequent infusions of cefiderocol 1.5 g q8h IV on Day 1 through Day 3. The dose of cefiderocol was changed to 2 g q8h due to renal function on Day 3, and the patient received 9 infusions at this dose level through Day 6. The patient was treated with caspofungin from Days -2 to 5.

On Day 3 (EA), the patient experienced the SAE of deterioration of respiratory functions during the night between Days 2 and 3 and the event of consciousness disorders. Chest x-ray was reported to show improvement with regression of right and left infiltrates and decrease of initial opacities. The patient was reintubated and put on a ventilator. The inflammatory indices of WBC count and body temperature were  $32.2 \times 10^9/\text{L}$  and 39.2°C, respectively. He recovered from the events on Day 4. The investigator considered the events moderate in severity and not related to study medication. The clinical outcome was indeterminate.

On Day 6 (EOT), the patient discontinued study treatment due to lack of efficacy. Chest x-ray was reported to show worsening with increase in size of the opacities. Signs and symptoms included moderate dyspnea (including retractions), expectorated sputum production, rhonchi, and severe fatigue. The inflammatory indices of WBC count and body temperature were  $26.3 \times 10^9/\text{L}$  and 36.8°C, respectively. No microbiological samples were collected. The patient was considered a clinical failure.

On Day 7, the patient was treated with amoxicillin-clavulanic acid.

On Day 11, the patient had SAEs of gastrointestinal haemorrhage and neurological failure. Following discussions with the family, the decision was made to stop active treatments. The patient was not on a ventilator.

On Day 12 (EOS), the inflammatory indices of WBC count, C-reactive protein (CRP), and body temperature were  $32.7 \times 10^9/\text{L}$ , 98 mg/L, and 37.9°C, respectively. The patient was reported to have died on Day 12 due to the SAE of deterioration in respiratory function. The SAEs of gastrointestinal haemorrhage and neurological failure were

ongoing at the time of death. The investigator considered the 3 SAEs unrelated to study medication.

**Table 1 Inflammatory Indices**

Visit	White Blood Cell Count (RR = 4.1 to 9.9)	C-reactive Protein (RR = 0 to 3)	Body Temperature
Screening/Baseline	24.1 × 10 <sup>9</sup> /L	NA	38.4°C
Early Assessment	32.2 × 10 <sup>9</sup> /L	NA	39.2°C
End of Treatment	26.3 × 10 <sup>9</sup> /L	NA	36.8°C
End of Study	32.7 × 10 <sup>9</sup> /L	98 mg/L	37.9°C

NA = not available; RR = reference range

**Table 2 Sequential Organ Failure Assessment Score Status**

Visit	SOFA Score
Screening/Baseline	8
End of Treatment	NA

NA = not available; SOFA = Sequential Organ Failure Assessment Infection Score

**Table 3 Antimicrobial Susceptibility Testing at Screening  
(European Committee on Antimicrobial Susceptibility Testing)**

Pathogen	Resistant	Intermediate	Susceptible	Not Applicable
<i>Enterobacter cloacae</i>	Aztreonam, cefepime, ceftazidime-avibactam, ceftolozane-tazobactam, ciprofloxacin, imipenem, meropenem	NA	Amikacin, colistin, tigecycline	Cefiderocol

NA = not applicable

**Table 4 Susceptibility Testing at Each Visit**

Visit	IHMA Organism ID	AMK	AZT	CFPM	CAZ/ AVI	CEF/ TAZ	CPFX	CST	IPM	MEPM	CFDC	TGC
		MIC µg/mL										
Screening/ Baseline	<i>Enterobacter cloacae</i> Sample ID E490099	8	> 32	> 16	> 64	> 64	> 4	1	32	64	16	1

AMK = amikacin; AZT = aztreonam; CAZ/AVI = ceftazidime-avibactam; CEF/TAZ = ceftolozane-tazobactam; CFDC = cefiderocol; CFPM = cefepime; CPFX = ciprofloxacin; CST = colistin; ID = identification; IHMA = International Health Management Associates; IPM = imipenem; MEPM = meropenem; MIC = minimum inhibitory concentration; TGC = tigecycline

**Table 5 Chest X-ray Results**

Visit	Lung Fields/ Airways	Heart/ Vessels	Other Structures	Comparison of Lung Fields to Screening
Screening/Baseline	Tracheal deviation to the right/Bilateral opacities and infiltrates predominant on the left side/ Subcutaneous emphysema on the right/Endotracheal tube/Nasogastric tube/Surgical staple	Normal	Normal	NA
Early Assessment	Regression of right and left infiltrates/Improved lunglights/decreases of the initial opacity	Normal	Normal	Improved
End of Treatment	Increases of the size of the opacity, already noticed on Day 3	Normal	Normal	Worsened

NA = not applicable

**Table 6 Liver Function Tests**

Visit	AST (RR = 15 to 37)	ALT (RR = 12 to 78)	ALP	GGT	Total Bilirubin (RR = 3 to 17)
Screening/Baseline	56 IU/L	35 IU/L	NA	NA	7 µmol/L
Early Assessment	50 IU/L	33 IU/L	NA	NA	9 µmol/L
End of Treatment	235 IU/L	198 IU/L	NA	NA	NA
End of Study	63 IU/L	83 IU/L	NA	NA	7 µmol/L

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase;

GGT = gamma-glutamyl transferase; NA = not available; RR = reference range

**Table 7 Renal Function Tests**

Visit	Blood Urea Nitrogen (RR = NA)	Serum Creatinine (RR = 59.2 to 104)	Creatinine Clearance (RR = NA)
Screening/Baseline	36.96 mmol/L	136 µmol/L	44.07 mL/min
Early Assessment	39.2 mmol/L	109 µmol/L	NA
End of Treatment	52.9 mmol/L	116 µmol/L	51.67 mL/min
End of Study	97.16 mmol/L	136 µmol/L	44.07 mL/min

NA = not available; RR = reference range

**Table 8 Coagulation Tests**

<b>Visit</b>	<b>Platelet Count (RR = 161 to 393)</b>	<b>aPTT (RR = 10.0 to 15.3)</b>	<b>PT-INR (RR = 0.0 to 1.2)</b>
Screening/Baseline	$201 \times 10^9/\text{L}$	NA	1.6
Early Assessment	$225 \times 10^9/\text{L}$	NA	1.1
End of Treatment	$286 \times 10^9/\text{L}$	83.3 sec	1.28
End of Study	$413 \times 10^9/\text{L}$	NA	1.22

aPTT = activated partial thromboplastin time; NA = not available; PT-INR = prothrombin international normalized ratio; RR = reference range

## Subject ID Patient # 21

Subject ID		Patient # 21		Country		Turkey	
Age		29		Clinical Diagnosis at Screening		BSI	
Gender		Female		Severity		Severe	
Race		White		APACHE II Score		24	
Height (cm)		170		Causative Pathogen at Screening		Acinetobacter baumannii	
Body Weight (kg)		70		CR Evidence at Screening (other than central lab)		Hospital antibiogram	
MIC of Meropenem		> 64 µg/mL		MIC of Cefiderocol		0.06 µg/mL	
MIC of Imipenem		> 64 µg/mL					
Duration of Study Treatment		6 days		Standard of Care		Tigecycline 50 mg IV, colistin 150 mg IV	
Study Drug		Cefiderocol (2 g q6h IV)					
Microbiological Results at TOC			Day 28 All-cause Mortality			Clinical Outcome at TOC	
Indeterminate			Death (Day 6)			NA	
Medical History (Ongoing)		Rectal carcinoma with metastasis to liver, lungs, left arm, and brain; malnutrition, tachycardia, hypothyroidism, kidney damage, shortness of breath, skin scar, anxiety, hypoalbuminemia, hypokalemia, anemia					
Medical History (Not Ongoing)		Emesis, xerophthalmia					
Adverse Event	Day	Severity	Action Taken with Study Drug	Outcome	Causality	Serious	
Hypotension	4	Moderate	Dose not changed	Recovering/ resolving	Not related	No	
Septic shock	5	Severe	Dose not changed	Fatal	Not related	Yes	
Hyperglycemia	5	Mild	Dose not changed	Recovering/ resolving	Not related	No	
Elevated liver function tests	6	Severe	Dose not changed	Not recovered/ not resolved	Not related	Yes	
Cardiac arrest	6	Severe	Dose not changed	Fatal	Not related	Yes	
Narrative Summary							
A 29-year-old White female from Turkey had a medical history of rectal cancer with metastases to the liver, lungs, left arm and brain. She underwent brain tumor surgery on an unknown date and received radiotherapy with chemotherapy for the following 6 months. Her last chemotherapy and radiotherapy. There was no history of any antibiotic use prior to hospitalization.							
She was admitted from an external center with a general condition deterioration and poor nutrition on Day -5. She was initially evaluated in the emergency department for difficulty breathing with deteriorating respiratory status and increasing dyspnea. She was intubated due to low PO <sub>2</sub> (value not provided), attached to mechanical ventilation and transferred to the ICU due to infection with a GCS score of 8. Renal failure was reported. Empirical antibiotics were given prior to randomization and were started with clarithromycin 500 mg twice a day, IV with ceftriaxone 1 g twice a day, IV.							

On Day -2, a high grade fever was reported. Blood culture sample taken on Day -2 identified pathogen (*A. baumannii*) that made the patient eligible for this study and showed the following local susceptibility results: ampicillin (R), gentamicin (S), ceftazidime (R), piperacillin-tazobactam (R), ciprofloxacin (R), imipenem (R), amikacin (S), meropenem (R), trimethoprim-sulfamethoxazole (R).

On Day -2, a clinical diagnosis of BSI was confirmed. The patient was consulted by the infectious disease team on Day -1, blood cultures grew carbapenem-resistant *A. baumannii*, and the patient was recruited to the study on Day -1. Empiric IV therapy was provided on Day -1 with teicoplanin 800 mg once, meropenem 1 g once, tigecycline 100 mg once, and colistin 300 mg once.

Her serum creatinine level was low on Day 1 and the PI reported that this was possibly due to long-term steroid treatment and chemotherapy. Clinical assessment was performed on Day 1, and the patient had severe signs and/or symptoms (not specified) of causative infection, and moderate chills/rigors. Blood sample showed the WBC was within normal range, and AST, ALP, ALT, GGT, LDH (1730 U/L, RR 135-214 U/L), CRP, and TBL were all elevated.

She was randomized into the cefiderocol arm and received cefiderocol from Day 1 to Day 6, 2 g q6h (CrCl was around 380 mL/min/1.73 m<sup>2</sup>).

On Day 4, she was evaluated for EA and blood cultures drawn from the jugular catheter grew carbapenem resistant *A. baumannii* and carbapenem resistant *Klebsiella pneumonia* (result on Day 7). At EA and the following few days, procalcitonin levels were at 7.8 ng/mL, 5.1 ng/mL, and 2 ng/mL, respectively. She was assessed to have had clinical failure.

The investigator reported that it seemed like her sepsis was gradually under control due to decreasing procalcitonin levels, but her platelet counts decreased and her blood pressure deteriorated. On Day 5, the unrelated SAE of septic shock was reported. On Day 5, methylprednisolone and thrombotic suspension were provided for the SAE of septic shock; dexamethasone was stopped on Day 6. Norepinephrine was provided for hypotension and the cardiac arrest. The SAE of elevated liver function tests was reported (Day 6). Blood results showed a high AST 141.9 U/L, ALT 42 U/L, TBL 2.44 mg/dL, and very low platelets  $21 \times 10^9/L$ . The causality of elevated liver function tests was reported to be not related to study drug but the investigator thought that the liver event occurred due to septic shock. The event of cardiac arrest was reported on Day 6 and the outcome of the septic shock and cardiac arrest were reported as Fatal. The patient died on Day 6 at 15:00 hours. The investigator considered the causality for the events of septic shock and cardiac arrest to be not related to study drug.

EOS visit was not completed as the patient died before EOT.

ALP = alkaline phosphatase; ALT = alanine aminotransferase; APACHE = Acute Physiology and Chronic Health Evaluation; AST = aspartate aminotransferase; BSI = blood stream infection; CR = carbapenem resistance/resistant; CrCl = creatinine clearance; CRP = C-reactive protein; EA = Early Assessment; eGFR = estimated glomerular filtration rate; EOS = End of Study; EOT = End of Treatment; GCS = Glasgow Coma Score; GGT = gamma-glutamyl transferase; ICU = intensive care unit; ID = identification; IV = intravenous; LDH = lactate dehydrogenase; MDRD = Modification of Diet in Renal Disease; MIC = mean inhibitory concentration; NA = not applicable; q6h = every 6 hours; PI = Principal Investigator; PO<sub>2</sub> = partial pressure of oxygen; R = resistant; S = susceptible; SAE = serious adverse event; TBL = total bilirubin; TOC = Test of Cure; WBC = white blood cell

**Study qualifying diagnosis:** Blood stream infection due to *A. baumannii* was identified to be CR through a hospital antibiogram (hospital epidemiology data showing CR rate > 90%).

**Study qualifying infection history:** On Day -1, *A. baumannii* resistant to ciprofloxacin, imipenem, and meropenem was identified from the blood samples taken on Day -2. *A. baumannii* was susceptible to amikacin and colistin (Table 3).

**Current hospitalization history:** The patient was hospitalized on Day -5 with breathing difficulty requiring intubation and was transferred to the ICU. The patient was placed on

synchronized intermittent mandatory ventilation (SIMV) on Day -5. The patient developed a high-grade fever on Day -2.

**Clinical course:** On Day -2, a microbiological laboratory specimen was obtained from the blood. Gram-negative rods (2+) were identified. The pathogen *A. baumannii* was identified. The patient was on a ventilator; arterial blood gases (ABGs) indicated PaO<sub>2</sub> was 32 mm Hg, PaCO<sub>2</sub> was 27 mm Hg, SaO<sub>2</sub> was 57%, and FiO<sub>2</sub> was 30%. The initial clinical assessment of signs and symptoms noted moderate chills/rigors and severe signs and symptoms of the causative infection (not specified). The Sequential Organ Failure Assessment (SOFA) score was 9. The inflammatory indices of WBC count, CRP, and body temperature were  $7.78 \times 10^9/\text{L}$ , 280.77 mg/dL, and 37.1°C, respectively.

Treatment with cefiderocol (2 g q6h IV) was initiated on Day 1. She received 19 subsequent doses of cefiderocol from Days 2 through 6.

On Day 4, a microbiological laboratory specimen was obtained from the blood. The pathogens *A. baumannii* and *K. pneumoniae* were identified from culture. The patient was on a ventilator; ABGs indicated PaO<sub>2</sub> was 32 mm Hg, PaCO<sub>2</sub> was 52 mm Hg, SaO<sub>2</sub> was 56%, and FiO<sub>2</sub> was 30%. Signs and symptoms showed mild chills/rigor and signs/symptoms of the causative infection. Clinical outcome was deemed to be clinical failure. The SOFA score was 9. The inflammatory indices of WBC count, CRP, and body temperature were  $6.21 \times 10^9/\text{L}$ , 378.68 mg/dL, and 38.0°C, respectively.

On Day 5, the patient experienced the SAE of severe septic shock. Treatment included methylprednisolone and thrombotic suspension. Norepinephrine was given for hypotension and cardiac arrest. The event was Fatal. The investigator considered the event not related to study drug.

On Day 6, the patient's vital signs reading included temperature of 38.5°C, blood pressure of 60/45 mm Hg, pulse rate of 135 beats per minute, and respiratory rate of 24 breaths per minute. The WBC count and CRP were  $13.96 \times 10^9/\text{L}$  and 349.95 mg/dL, respectively. The patient died on Day 6 due to the SAE of septic shock, which was the same day the patient received her last dose of study drug.

**Table 1**                      **Inflammatory Indices**

Visit	White Blood Cell Count (RR = 4.4 to 11.3)	C-reactive Protein (RR = 0 to 5)	Body Temperature
Screening/Baseline	$7.78 \times 10^9/\text{L}$	280.77 mg/dL	37.1°C
Early Assessment	$6.21 \times 10^9/\text{L}$	378.68 mg/dL	38.0°C
End of Treatment	$13.96 \times 10^9/\text{L}$	349.95 mg/dL	38.5°C

RR = reference range

**Table 2 Sequential Organ Failure Assessment Score Status**

Visit	SOFA Score
Screening/Baseline	9
Early Assessment	9

SOFA = Sequential Organ Failure Assessment

**Table 3 Antimicrobial Susceptibility Testing at Screening  
(European Committee on Antimicrobial Susceptibility Testing)**

Pathogen	Resistant	Intermediate	Susceptible	Not Applicable
<i>Acinetobacter baumannii</i>	Ciprofloxacin, imipenem, meropenem	NA	Amikacin, colistin	Aztreonam, ceftazidime-avibactam, ceftolozane-tazobactam, cefiderocol, tigecycline, cefepime

NA = not applicable

**Table 4 Susceptibility Testing at Each Visit**

Visit	IHMA Organism ID	AMK	AZT	CFPM	CAZ/AVI	CEF/TAZ	CPFX	CST	IPM	MEPM	CFDC	TGC
		MIC µg/mL										
Screening/ Baseline	<i>Acinetobacter baumannii</i> Sample ID E784711	≤ 4	> 32	8	32	4	> 4	1	> 64	> 64	0.06	1
Early Assessment	<i>Acinetobacter baumannii</i> Sample ID E784705	≤ 4	> 32	16	32	8	> 4	1	> 64	> 64	0.12	1

AMK = amikacin; AZT = aztreonam; CAZ/AVI = ceftazidime-avibactam; CEF/TAZ = ceftolozane-tazobactam; CFDC = cefiderocol; CFPM = cefepime; CPFX = ciprofloxacin; CST = colistin; ID = identification; IHMA = International Health Management Associates; IPM = imipenem; MEPM = meropenem; MIC = minimum inhibitory concentration; TGC = tigecycline

**Table 5 Liver Function Tests**

Visit	AST (RR = 0 to 32)	ALT (RR = 0 to 33)	ALP (RR = 35 to 104)	GGT (RR = 6 to 42)	Total Bilirubin (RR = 0 to 1.2)
Screening/Baseline	84.1 U/L	46.7 U/L	487 U/L	213 U/L	1.68 mg/dL
Early Assessment	128.7 U/L	51 U/L	410 U/L	177 U/L	1.97 mg/dL
End of Treatment	141.9 U/L	42.2 U/L	NA	NA	2.44 mg/dL

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase;  
GGT = gamma-glutamyl transferase; NA = not available; RR = reference range

**Table 6 Renal Function Tests**

Visit	Blood Urea Nitrogen (RR = 6 to 20)	Serum Creatinine (RR = 28 to 217)	Creatinine Clearance
Screening/Baseline	16.8 mg/dL	0.17 mg/dL	539.58 mL/min
Early Assessment	16.5 mg/dL	0.08 mg/dL	1146.61 mL/min
End of Treatment	NA	0.31 mg/dL	295.90 mL/min

RR = reference range

**Table 7 Coagulation Tests**

Visit	Platelet Count (RR = 154 to 386)	aPTT (RR = 24 to 35)	PT-INR (RR = 0.8 to 1.2)
Screening/Baseline	$40 \times 10^9/L$	14.4 sec	1.15
Early Assessment	$12 \times 10^9/L$	39.5 sec	1.19
End of Treatment	$21 \times 10^9/L$	31.7 sec	1.59

aPTT = activated partial thromboplastin time; PT-INR = prothrombin international normalized ratio;  
RR = reference range

## Subject ID Patient # 22

Subject ID		Patient # 22	Country		Israel	
Age		69	Clinical Diagnosis at Screening		VAP	
Gender		Male	Severity		Severe	
Race		White	APACHE II Score		13	
Height (cm)		180	Causative Pathogen at Screening		Acinetobacter baumannii	
Body Weight (kg)		80	CR Evidence at Screening (other than central lab)		Treatment failure CR-GNB	
MIC of Meropenem		64 µg/mL	MIC of Cefiderocol		1.0 µg/mL	
MIC of Imipenem		64 µg/mL				
Duration of Study Treatment		9 days	Standard of Care		Colistin (3 mEq, IV)	
Study Drug		Cefiderocol (1 to 2 g, q8h; 0.75 g, IV q12h)				
Microbiological Results at TOC		Day 28 All-cause Mortality			Clinical Outcome at TOC	
Indeterminate		Death (Day 9)			Clinical failure (EA)	
Medical History (Ongoing)	Vocal cord paralysis, COPD, intermittent constipation, BPH; dyslipidemia; ischemic heart disease; hypertension, atrial fibrillation; contusion of chest and chest wall; diabetes mellitus; bronchoscopy with trans-bronchial biopsy; anemia, pulmonary hemorrhage; sepsis; finger ischemia and septic shock; chest tube					
Medical History (Not Ongoing)	Meningioma, mitral valve repair; long-term use of aspirin, post-surgical aortocoronary bypass ; pneumonia; hemothorax; pneumonia; Escherichia coli blood; left lung atelectasis; hyperkalemia, pleural effusion					
Adverse Event	Day	Severity	Action Taken with Study Drug	Outcome	Causality	Serious
Acute renal failure creatinine = 1.37	1	Moderate	Not available	Not recovered/ not resolved	Not available	No
Candida tropicalis - blood	3	Mild	Dose not changed	Not recovered/ not resolved	Not related	No
Restlessness	4	Mild	Dose not changed	Recovered/ resolved	Not related	No
Diarrhea	5	Mild	Dose not changed	Recovered/ resolved	Not related	No
Pressure sore of buttocks, stage 1, and one pressure sore	5	Mild	Dose not changed	Not recovered/ not resolved	Not related	No
Vomit	6	Mild	Dose not changed	Recovered/ resolved	Not related	No
Elevated liver function AST = 660 U/L	7	Severe	Dose not changed	Not recovered/ not resolved	Not related	No

Serotic sores (pressure ulcer)	7	Moderate	Dose not changed	Not recovered/ not resolved	Not related	No
Non resolved sepsis worsening	9	Severe	Dose not changed	Fatal	Not related	Yes

#### Narrative Summary

A 69-year-old white male from Israel had a medical history of ischemic heart disease, atrial fibrillation, contusion of chest wall and DM, long-term use of aspirin and post-surgical aortocoronary bypass.

Patient was admitted on Day -23 to the general ward from home for dyspnea and “respiratory abnormality”. On Day -20, severe VAP was diagnosed. On the same day, he underwent a workup for lung malignancy which included a bronchoscopy with a trans-bronchial biopsy; results showed fragments of the wall of the large bronchus containing cartilage with mild chronic and acute inflammatory infiltrates and a small lymphoid aggregate, no evidence of malignancy and no lung tissue present. During the procedure, he deteriorated, developed iatrogenic complications, and was mechanically ventilated. On Day -18, the patient was discharged home.

On Day -16, the patient was again admitted (emergent) due to pulmonary hemorrhage. It was reported that he developed a hemothorax after the trans-bronchial biopsy and the iatrogenic complication led to his current infection on which he was enrolled. He was treated for pneumonia with various antibiotics including ceftriaxone from Day -15 to Day -14, respectively) and piperacillin-tazobactam on Day -13. The patient had a primary septic bout of ESBL-producing *E. coli* BSI. Treatment included ertapenem (Day -13 to Day -12 and Day -7 to Day -5). On Day -11, the patient was attached to mechanical ventilation (SIMV) and was weaned off the following day. On Day -5, the patient was transferred to the ICU, again placed on mechanical ventilation (SIMV), and treated with meropenem (Day -5 to Day -2) and norepinephrine for sepsis (Day -5). Treatment also included vancomycin (Day -5 to Day 1) and colistin (Day -3 to Day 1). At the time of enrollment, this episode of BSI was long resolved (resolution date not reported). On Day -3, pleural fluid sample was taken, and *A. baumannii* was identified. On Day -4, the patient was in septic shock.

On Day 1, the event of ARF was reported. Causality and action taken with study drug were not reported. The event of ARF was ongoing at the time of patient’s death.

On Day 1, the patient was recruited into this study with VAP. He was randomized and study drug was started and provided until Day 9; the dose of study drug started with maximum recommended dose and after 1 day was adjusted for renal function and had subsequent adjustments until EOT. Clinical assessment showed severe fatigue, malaise, and suctioned respiratory secretions; moderate rales, rhonchi, cough, expectorated sputum production, and dullness on percussion; and mild dyspnea (including retractions) and wheezing. Chest x-ray showed right lower lobe infiltrate; patient continued on mechanical ventilation.

Sputum culture obtained at the unscheduled visit, Day 2 showed *A. baumannii*. On Day 3, EA visit, chest x-ray showed worsening lung fields in comparison to Screening (bilateral infiltrates in the lower lobes [right greater than left]). Clinical outcome showed clinical failure. On Day 3, the AE of *Candida tropicalis*-blood was reported (mild) and treated with micafungin.

On Day 7 (Unscheduled Visit), clinical assessment showed severe fatigue, malaise, and suctioned respiratory secretions. The following symptoms occurred newly since Baseline: cough, severe expectorated sputum production, dyspnea (including retractions), wheezing, rales, rhonchi, and dullness on percussion. Chest x-ray results were not available. Sputum culture was obtained (Day 6) and *A. baumannii* was identified. On Day 7, the event of elevated liver AST 660 U/L was reported (severe), which was considered not related to study drug by the investigator. Action taken was dose not changed and the outcome of the event was not recovered/not resolved. Sputum culture showed *A. baumannii*. On Day 9, EOT occurred because the SAE of non-resolved sepsis worsening (severe) was reported, and the patient died due to sepsis on the same day. Clinical outcome was provided as clinical failure at EOT, as EOT was unexpected because of the patient’s sudden death. The investigator reported that prior to the sudden death, the patient deteriorated despite continuous treatment and maximal supportive therapy due to his pre-existing serious conditions prior to enrollment, he never improved. The investigator further

reported that initially he showed some signs of improvement, but later developed central-line associated candidemia (verbatim: “*C. tripicalis* - blood”). During hospitalization, *A. baumannii* persisted in sputum. He developed acute kidney injury (hemodialysis initiated), thrombocytopenia and multi-organ failure. The patient never improved and expired on Day 9. The patient’s death was not attributed to the study drug.

AE = adverse event; APACHE = Acute Physiology and Chronic Health Evaluation; ARF = acute renal failure; AST = aspartate aminotransferase; BSI = blood stream infection; BPH = benign prostatic hypertrophy; COPD = chronic obstructive pulmonary disease; CR = carbapenem resistant; EA = Early Assessment; EOT = End of Treatment; ESBL = extended spectrum beta-lactamases; ICU = intensive care unit; ID = identification; IV = intravenous; mEq = milli equivalent; MIC = minimum inhibitory concentration; NA = not available; q8h = every 8 hours; q12h = every 12 hours; SAE = serious adverse event; SIMV = synchronized intermittent mandatory ventilation; TOC = Test of Cure; unk = unknown; VAP = ventilator-associated pneumonia

**Study qualifying diagnosis:** Ventilator-associated pneumonia (onset Day -21) due to *A. baumannii* was identified with evidence of CR through treatment failure.

**Study qualifying infection history:** On Day 1, *A. baumannii* resistant to amikacin, ciprofloxacin, imipenem, and meropenem was identified from the pleural fluid. The isolate was susceptible to colistin (Table 3).

In parallel with this identification, the patient was treated for pneumonia with various antibiotics including ceftriaxone from Day -15 to Day -14 and piperacillin-tazobactam on Day -13. The patient had a primary septic bout of ESBL-producing *E. coli* BSI. Treatment included ertapenem on Day -13 to Day -12 and Day -7 to Day -5, meropenem on Day -5 to Day -2, norepinephrine for sepsis on Day -5, vancomycin on Day -5 to Day 1, and colistin on Day -3 to Day 1.

**Current hospitalization history:** The patient was hospitalized on Day -16 from home as an emergent admission into the ICU due to hemothorax. The patient was placed on ventilation (SIMV) on Day -11 through Day -10 and again on Day -5 through Day 9. The patient was subsequently transferred to isolation on Day -3. The onset date of VAP was Day -20.

**Clinical course:** On Day -3, a microbiological laboratory sample was obtained from the pleural fluid. The pathogen *A. baumannii* (no quantitation) was identified.

On Day -2, a microbiological laboratory sample was obtained from the sputum. White blood cell (WBC) polymorphs (2+, 10 to 24, moderate) and squamous epithelial cells (1+, <10, few) were noted. The pathogen *A. baumannii* was isolated.

On Day 1 (Screening/Baseline), the chest radiograph showed right lower lobe infiltrates (Table 5). The patient was on ventilator; arterial blood gases (ABGs) indicated PaO<sub>2</sub> 101 mm Hg, PaCO<sub>2</sub> 44 mm Hg, SaO<sub>2</sub> 97%, and FiO<sub>2</sub> 51%. The initial clinical assessment of signs and symptoms revealed mild dyspnea (including retractions) and wheezing; moderate cough, expectorated sputum production, rales, rhonchi, and dullness upon percussion; and severe fatigue, malaise, and suctioned respiratory secretions. The Sequential Organ Failure Assessment (SOFA) score was 11, and the Clinical Pulmonary Infection Score (CPIS) was 4 (Table 2). The inflammatory indices WBC count,

C-reactive protein (CRP), and body temperature were  $10.6 \times 10^9/L$ , 439.48 mg/L, and  $37^\circ C$ , respectively (Table 1). On the same day, microbiological laboratory samples were obtained from the sputum and blood; and Gram-negative bacteria were identified (+-) and (-+) in the blood sample. The sputum sample showed no gram negative bacteria.

The patient received his first dose of cefiderocol (2 g, q8h) on Day 1 and he received 20 subsequent doses of cefiderocol (2 g q8h, 1.5 g q8h, 0.75 g q12h, and 1 g q8h), through Day 9. The dose of cefiderocol was adjusted multiple times due to the patient's renal profile.

On Day 2 (Unscheduled Visit), a microbiological laboratory sample was obtained from the sputum, and WBC polymorphs (2+, 10 to 24, moderate) and squamous epithelial cells (1+, < 10, few) were noted. The pathogen *A. baumannii* (no quantitation) was identified. The inflammatory index of body temperature was  $37^\circ C$ .

On Day 3 (EA), a microbiological laboratory sample was obtained from the sputum and WBC polymorphs (2+, 10 to 24, moderate) were noted. The pathogen *A. baumannii* (no quantitation) was identified. The chest radiograph showed bilateral infiltrates in the lower lobes, right greater than left; and lung fields in comparison to Screening had worsened. The patient was on a ventilator; ABGs indicated PaO<sub>2</sub> 92 mm Hg, PaCO<sub>2</sub> 54 mm Hg, SaO<sub>2</sub> 97%, and FiO<sub>2</sub> 38%. Signs and symptoms included mild wheezing and dyspnea (including retractions); moderate cough, expectorated sputum production, rales, rhonchi, and dullness on percussion; and severe fatigue, malaise, and suctioned respiratory secretions. The SOFA score was 12, and the CPIS was 4. The inflammatory indices of WBC count, CRP, and body temperature were  $9.0 \times 10^9/L$ , 268.85 mg/L, and  $37^\circ C$ , respectively. The patient was considered a clinical failure.

The patient experienced the AE of *Candida tropicalis*-blood on Day 3. The dose of study drug was not changed due to the event. Treatment for the event included micafungin. The patient did not recover from the event. The investigator considered the event mild and not related to the study drug.

On Day 6, a microbiological laboratory sample was obtained from the sputum, and WBC polymorphs (2+, 10 to 24, moderate) and squamous epithelial cells (1+, < 10, few) were noted. The pathogen *A. baumannii* (no quantitation) was identified.

On Day 7 (Unscheduled Visit), a microbiological laboratory sample was obtained from the sputum, and WBC polymorphs (1+, < 10, few) and squamous epithelial cells (1+, < 10, few) were noted. The pathogen *A. baumannii* (no quantitation) was identified. The patient was on a ventilator; ABGs indicated PaO<sub>2</sub> 89 mm Hg, PaCO<sub>2</sub> 43 mm Hg, SaO<sub>2</sub> 97%, and FiO<sub>2</sub> 34%. Signs and symptoms included severe fatigue, malaise, and dyspnea (including retractions), expectorated sputum production, and suctioned respiratory secretions, wheezing, rales, rhonchi, and dullness on percussion. The inflammatory indices of WBC count, CRP, and body temperature were  $13.1 \times 10^9/L$ , 179.19 mg/L, and  $36.5^\circ C$ , respectively.

On Day 7, the AE of elevated liver function AST 660 U/L was reported (severe), which was considered not related to study drug by the investigator. Other laboratory values included alanine aminotransferase (ALT) 150 U/L, alkaline phosphatase (ALP) 246 U/L, and total bilirubin 0.36 mg/dL. The action taken was dose not changed, and the outcome of the event was not recovered/not resolved.

On Day 9 (EOT), the patient was on a ventilator; ABGs indicated PaO<sub>2</sub> 43 mm Hg, PaCO<sub>2</sub> 60 mm Hg, SaO<sub>2</sub> 95%, and FiO<sub>2</sub> 69%. The inflammatory indices of WBC count, CRP, and body temperature were  $8.0 \times 10^9$ /L, 208.63 mg/L, and 36.3°C, respectively. The patient experienced the SAE of non-resolved sepsis worsening. The dose of study drug was not changed. The investigator considered the event severe and not related to the study drug. On the same day, the patient died before completing treatment due to the SAE; this was also the same day he received his last dose of study drug. No clinical or microbiological outcomes were provided on EOT, as EOT was unexpected because of sudden death.

**Table 1 Inflammatory Indices**

Visit	White Blood Cell Count (RR = 4 to 11)	C-reactive Protein (RR = 0.3 to 5)	Body Temperature
Screening/Baseline	$10.6 \times 10^9$ /L	439.48 mg/L	37.0°C
Early Assessment	$9.0 \times 10^9$ /L	268.85 mg/L	37.0°C
Unscheduled Visit (Day 7)	$13.1 \times 10^9$ /L	179.19 mg/L	36.5°C
End of Treatment	$8.0 \times 10^9$ /L	208.63 mg/L	36.3°C

**Table 2 Sequential Organ Failure Assessment and Total Clinical Pulmonary Infection Score Status**

Visit	SOFA Score	Total CPIS
Screening/Baseline	11	4
Early Assessment	12	4

CPIS = Clinical Pulmonary Infection Score; SOFA = Sequential Organ Failure Assessment

**Table 3 Antimicrobial Susceptibility Testing at Screening (European Committee on Antimicrobial Susceptibility Testing)**

Pathogen	Resistant	Intermediate	Susceptible	Not Applicable
<i>Acinetobacter baumannii</i>	Amikacin, ciprofloxacin, imipenem, meropenem	NA	Colistin	Aztreonam, ceftazidime- avibactam, ceftolozane- tazobactam, cefiderocol, tigecycline, cefepime

NA = not applicable

**Table 4**                      **Susceptibility Testing at Each Visit**

Visit	IHMA Organism ID	AMK	AZT	CFPM	CAZ/ AVI	CEF/ TAZ	CPFX	CST	IPM	MEPM	CFDC	TGC
		MIC µg/mL										
Screening/ Baseline	<i>Acinetobacter baumannii</i> Sample ID E833131	> 64	> 32	> 16	64	> 64	> 4	2	64	64	1	0.5

AMK = amikacin; AZT = aztreonam; CAZ/AVI = ceftazidime-avibactam; CEF/TAZ = ceftolozane-tazobactam; CFDC = cefiderocol; CFPM = cefepime; CPFX = ciprofloxacin; CST = colistin; ID = identification; IHMA = International Health Management Associates; IPM = imipenem; MEPM = meropenem; MIC = minimum inhibitory concentration; TGC = tigecycline

**Table 5 Chest Radiograph Results**

Visit	Lung Fields/ Airways	Heart/ Vessels	Other Structures	Comparison of Lung Fields to Screening
Screening/Baseline	Right lower lobe infiltrates	NA	NA	NA
Early Assessment	Bilateral infiltrates lower lobes (right > left)	NA	NA	Worsened

NA = not applicable

**Table 6 Liver Function Tests**

Visit	AST (RR = 5 to 38)	ALT (RR = 4 to 41)	ALP (RR = 39 to 117)	GGT (RR = 10 to 55)	Total Bilirubin (RR = 0.2 to 1.2)
Screening/Baseline	92 U/L	41 U/L	269 U/L	23 U/L	0.76 mg/dL
Early Assessment	102 U/L	38 U/L	345 U/L	34 U/L	0.24 mg/dL
Unscheduled Visit (Day 7)	660 U/L	150 U/L	246 U/L	NA	0.36 mg/dL
End of Treatment	NA	NA	NA	NA	0.32 mg/dL

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase;  
GGT = gamma-glutamyl transferase; NA = not available

**Table 7 Renal Function Tests**

Visit	Blood Urea Nitrogen (RR = 20 to 45)	Serum Creatinine (RR = 0.7 to 1.2)	Creatinine Clearance
Screening/Baseline	23.8 mg/dL	1.07 mg/dL	73.73 mL/min
Early Assessment	51.1 mg/dL	2.03 mg/dL	38.86 mL/min
Unscheduled Visit (Day 7)	65.1 mg/dL	2.28 mg/dL	NA
End of Treatment	82.6 mg/dL	2.57 mg/dL	30.70 mL/min

NA = not available

**Table 8 Coagulation Tests**

Visit	Platelet Count (RR = 140 to 450)	aPTT (RR = 23 to 36)	PT-INR (RR = 0.84 to 1.17)
Screening/Baseline	$64 \times 10^9/L$	29.8 sec	1.02
Early Assessment	$18 \times 10^9/L$	31.3 sec	0.98
Unscheduled Visit (Day 7)	$30 \times 10^9/L$	NA	NA
End of Treatment	$18 \times 10^9/L$	NA	NA

aPTT = activated partial thromboplastin time; NA = not available; PT-INR = prothrombin international normalized ratio

## Subject ID Patient # 23

Subject ID	Patient # 23	Country	Israel		
Age	65	Clinical Diagnosis at Screening	VAP		
Gender	Male	Severity	Moderate		
Race	White	APACHE II Score	27		
Height (cm)	165.0	Causative Pathogens at Screening	Acinetobacter baumannii, Pseudomonas aeruginosa		
Body Weight (kg)	63.0	CR Evidence at Screening (other than central lab)	Treatment failure CR-GNB		
MIC of Meropenem	32 µg/mL, A. baumannii; 16 µg/mL, P. aeruginosa	MIC of Cefiderocol	1 µg/mL, A. baumannii; 0.5 µg/mL, P. aeruginosa		
MIC of Imipenem	32 µg/mL, A. baumannii; 16 µg/mL, P. aeruginosa				
Duration of Study Treatment	11 days	Standard of Care	Tigecycline 100 mg IV		
Study Drug	Cefiderocol 1 to 1.5g q8h IV				
Microbiological Results at TOC		Day 28 All-cause Mortality	Clinical Outcome at TOC		
Persistence (EOT)		Death (Day 13)	Clinical failure (EOT)		
Medical History (Ongoing)	Malignant neoplasm of bronchus and lung, adenocarcinoma, solitary pulmonary nodule, COPD, tuberculosis, septic shock, mechanical ventilation; renal failure, sepsis, anxiety, congestive heart failure; intermediate constipation				
Medical History (Not Ongoing)	Tuberculosis, thorascopic lobectomy of lung, thoracotomy exploratory, septic shock, esophagectomy, mediastinitis, perforation of esophagus, proximal gastrectomy, laparotomy, pulmonary insufficiency, fever, tracheostomy, hemodialysis, vomit				
Adverse Event	Day	Severity	Action Taken with Study Drug	Outcome	Serious
Edema	1	Moderate	Dose not changed	Not recovered/ not resolved	No
Fever	2	Mild	Dose not changed	Recovered/ resolved	No
Acute renal failure	2	Severe	Dose not changed	Not recovered/ not resolved	No
Diarrhea	3	Mild	Dose not changed	Not recovered/ not resolved	No
Pressure ulcer class 2	5	Moderate	Dose not changed	Not recovered/ not resolved	No
Leukocytosis	7	Moderate	Dose not changed	Not recovered/ not resolved	No
Low blood pressure	7	Severe	Dose not changed	Not recovered/ not resolved	No
Anemia	7	Mild	Dose not changed	Not recovered/ not resolved	No

Tachycardia	8	Moderate	Dose not changed	Not recovered/ not resolved	No
Septic shock worsening	8	Severe	Dose not changed	Not recovered/ not resolved	No
Fever	11	Moderate	Dose not changed	Not recovered/ not resolved	No
Hypothermia	13	Moderate	NA	Not recovered/ not resolved	No
Unresolved sepsis	13	Severe	NA	Fatal	Yes

#### **Narrative Summary**

A 65-year-old male from Israel with a history of tuberculosis had adenocarcinoma of the right bronchus/lung (adenocarcinoma), thoracoscopic lobectomy of right lung, solitary right pulmonary nodule (adenocarcinoma), and COPD, tuberculosis.

On Day -62, the patient was admitted emergently (to ICU) for perforation of the esophagus with severe mediastinitis and was in septic shock. It was reported that the patient had a lung malignancy and esophageal perforation for which no definite surgical solution could be achieved and suffered from several bouts of respiratory infections.

On the same day, Day -62, the patient underwent surgical treatment which included a right exploratory thoracotomy with esophagectomy and laparotomy with a proximal gastrectomy and transferred back to ICU. On Day -61, the patient experienced pulmonary insufficiency and was attached to mechanical ventilation. He was treated initially empirically with a combination of vancomycin, meropenem, and fluconazole. The patient developed a fever and was in renal failure on the same date (Day -60).

Treatment with colistin was added on Day -57. Tigecycline, piperacillin-tazobactam, levofloxacin, meropenem, and vancomycin were used to treat sepsis. Fluconazole was provided for the esophagectomy. In addition, sulfamethoxazole/trimethoprim was given for sepsis.

On Day -38, a tracheostomy was performed. On Day -33, a combination of vancomycin (until Day -28), meropenem (until Day -26), fluconazole and colistin (until Day -26) were provided for sepsis.

On Day -29, the patient underwent hemodialysis and was in CHF on Day -25. On Day -18, ceftazidime was provided until Day -7.

On Day -3, the patient developed VAP. Tigecycline was provided for 2 days.

On Day 1, the patient was enrolled in the study and randomized to the cefiderocol arm (Day 1 to Day 13) with diagnosis of VAP. Standard susceptibility testing showed Treatment failure CR-GNB. Chest x-ray showed bilateral infiltrates. Sputum cultures collected on Days -21 and -1 showed *A. baumannii* and *P. aeruginosa*. Cefiderocol was started. The unrelated AE of edema (moderate) and unrelated fever (mild) was reported on Day 1.

On Day 2, the unrelated AE of acute renal failure (severe) was reported.

On Day 4, at EA visit, the patient had persisting symptoms. Chest x-ray completed on Day 5 showed worsening from Screening. Clinical outcome was reported as clinical failure. On the next day, the unrelated AE of pressure ulcer class 2 (moderate) was reported. On Day 7, the unrelated AE of low blood pressure was reported (severe).

On Day 8, the unrelated AE of septic shock worsening was reported (severe). On Day 9 (unscheduled visit), creatinine was at 2.84 mg/dL.

On Day 11, EOT was completed. Clinical signs and symptoms persisted. Inflammatory markers did not improve, and chest x-ray results showed worsening. The investigator reported that the patient's treatment was discontinued after he completed 11 days on protocol. The patient experienced a leukemoid reaction (WBC count at  $50 \times 10^9/L$ ) with acute diarrhea (serological test for *Clostridium difficile* was negative); therefore, the antibiotic treatment was discontinued. No antibiotic was given after Day 11. The patient's condition continued to deteriorate and the unrelated AE of fever was reported (moderate). Sputum cultures continued to grow XDR *A. baumannii* (on Day 12). Clinical and microbiological outcomes showed clinical failure and persistence, respectively.

On Day 13, the unrelated AE of hypothermia was reported (moderate). The patient expired on the same day due the SAE of unresolved sepsis (severe) (due to XDR *A. baumannii* pneumonia).

AE = adverse event; APACHE = Acute Physiology and Chronic Health Evaluation; CHF= congestive heart failure; COPD = chronic obstructive pulmonary disease; CR = carbapenem resistance; CT = computed tomography; EA = Early Assessment; EOT = End of Treatment; GNB = Gram-negative bacteria; ICU= intensive care unit; ID = identification; MIC = minimum inhibitory concentration; SAE = serious adverse event; TOC = Test of Cure; unk = unknown; XDR= extensively drug-resistant; VAP = ventilator-associated pneumonia; WBC = white blood cell

**Study qualifying diagnosis:** Ventilator-associated pneumonia due to *A. baumannii* and *P. aeruginosa* identified to be carbapenem resistant through treatment failure CR-GNB.

**Study qualifying infection history:** On Day -2, *A. baumannii* resistant to amikacin, ciprofloxacin, imipenem, and meropenem was identified from the sputum. The isolate was susceptible to colistin. On the same day, *P. aeruginosa* resistant to cefepime, aztreonam, imipenem, and meropenem was identified from the sputum (Table 3). The isolate was susceptible to amikacin, ceftazidime-avibactam, ceftolozane-tazobactam, ciprofloxacin, and colistin.

**Current hospitalization history:** The patient was hospitalized on Day -62 from an acute care treatment facility as an emergent admission onto the intensive care unit (ICU) due to perforation of the esophagus. The patient underwent surgical treatment; right exploratory thoracotomy with esophagostomy and laparotomy with a proximal gastrectomy. On Day -62, the patient started on mechanical ventilation. Synchronized intermittent mandatory ventilation was initiated on Day -62 and continued through the patient's death on Day 13. The onset date of infection was Day -3.

**Clinical course:** On Day -2, a microbiological laboratory sample was obtained from the sputum and WBC polymorphs (3+,  $\geq 25$ , many) were noted. The pathogens *A. baumannii* (no quantitation) and *P. aeruginosa* (no quantitation) were identified.

On Day -1, a microbiological laboratory sample was obtained from the sputum, and WBC polymorphs (1+,  $< 10$ , few) were noted. The pathogens *A. baumannii* (no quantitation) and *P. aeruginosa* (no quantitation) were identified.

On Day 1 (Screening/Baseline), the chest radiograph showed bilateral infiltrates in the lung fields and airways (Table 5). The patient was on a ventilator; arterial blood gases (ABGs) indicated PaO<sub>2</sub> 222 mm Hg, PaCO<sub>2</sub> 57 mm Hg, SaO<sub>2</sub> 95%, and FiO<sub>2</sub> 50%. The initial clinical assessment of signs and symptoms revealed moderate cough, dyspnea (including retraction), wheezing; and severe expectorated sputum production, suctioned respiratory secretions, rales, rhonchi, dullness on percussion and bronchial breath sounds. The Sequential Organ Failure Assessment (SOFA) score was 6 and the Clinical Pulmonary Infection Score (CPIS) was 5 (Table 2). The inflammatory indices of WBC count, C-reactive protein (CRP), and body temperature were  $32.8 \times 10^9/L$ , 116.52 mg/L, and 37.2°C, respectively (Table 1).

The patient received his first dose of cefiderocol (1 g, IV, q8h) on Day 1 and he received 8 subsequent doses through Day 4. He received cefiderocol (1.5 g, IV, q8h) on Day 4 and

he received 14 subsequent doses through Day 9. The patient received cefiderocol (1 g, IV, q8h) on Day 9 and he received 5 subsequent doses through Day 11.

On Day 4 (EA), a microbiological laboratory sample was obtained from the sputum, and WBC polymorphs (1+, < 10, few) were noted. The pathogens *A. baumannii* (no quantitation) and *P. aeruginosa* (no quantitation) were identified. The patient was on a ventilator; ABGs indicated PaO<sub>2</sub> 183 mm Hg, PaCO<sub>2</sub> 35 mm Hg, SaO<sub>2</sub> 100%, and FiO<sub>2</sub> 50%. Signs and symptoms revealed moderate cough, dyspnea (including retractions), wheezing; and severe expectorated sputum production, suctioned respiratory secretions, rales, rhonchi, dullness on percussion and bronchial breath sounds. The SOFA score was 6 and the CPIS was 5. The inflammatory indices of WBC count, CRP, and body temperature were  $23.7 \times 10^9/L$ , 223 mg/L, and 37.1°C, respectively. The patient was considered a clinical failure.

On Day 5, the chest radiograph showed bilateral small infiltrates and minor pleural effusion right lung, and the lung fields in comparison to Screening had worsened.

On Day 8, the patient experienced the AE of septic shock worsening. The dose of study medication was not changed. The patient did not recover from the event. The investigator considered the event severe and not related to study medication.

On Day 10 (Unscheduled Visit), a microbiological laboratory sample was obtained from the sputum, and WBC polymorphs (3+, ≥ 25, many) were noted. The pathogen *A. baumannii* (no quantitation) was identified.

On Day 11 (EOT), a microbiological laboratory sample was obtained from the sputum and WBC polymorphs (3+, ≥ 25, many) and squamous epithelial cells (1+, < 10, few) were noted. The pathogen *A. baumannii* (no quantitation) was identified. The patient was on a ventilator; ABGs indicated PaO<sub>2</sub> 71 mm Hg, PaCO<sub>2</sub> 803 mm Hg, SaO<sub>2</sub> 100%, and FiO<sub>2</sub> 50%. Signs and symptoms revealed moderate cough, dyspnea (including retractions), wheezing; and severe expectorated sputum production, suctioned respiratory secretions, rales, rhonchi and dullness on percussion and bronchial breath sounds. The SOFA score was 14 and the CPIS was 8. The inflammatory indices of WBC count, CRP, and body temperature were  $49.9 \times 10^9/L$ , 91.84 mg/L, and 38.6°C, respectively. The patient was considered a clinical failure with a microbiological outcome of persistence (assessed on Day 12).

On Day 12, the chest radiograph showed bilateral small infiltrates and minor pleural effusion right lung, and the lung fields' comparison to Screening had worsened.

On Day 13, the patient experienced the SAE of unresolved sepsis. The event was fatal. The investigator considered the event severe and not related to study medication. The patient died due to the SAE of unresolved sepsis on Day 13, 2 days after receiving his last dose of study medication.

**Table 1 Inflammatory Indices**

Visit	White Blood Cell Count (RR = 4 to 11)	C-reactive Protein (RR = 0.3 to 5)	Body Temperature
Screening/Baseline	$32.8 \times 10^9/L$	116.52 mg/L	37.2°C
Early Assessment	$23.7 \times 10^9/L$	223 mg/L	37.1°C
End of Treatment	$49.9 \times 10^9/L$	91.84 mg/L	38.6°C

RR = reference range

**Table 2 Sequential Organ Failure Assessment and Total Clinical Pulmonary Infection Score Status**

Visit	SOFA Score	Total CPIS
Screening/Baseline	6	5
Early Assessment	6	5
End of Treatment	14	8

CPIS = Clinical Pulmonary Infection Score; SOFA = Sequential Organ Failure Assessment

**Table 3 Antimicrobial Susceptibility Testing at Screening (European Committee on Antimicrobial Susceptibility Testing)**

Pathogen	Resistant	Intermediate	Susceptible	Not Applicable
<i>Acinetobacter baumannii</i>	Amikacin, ciprofloxacin, imipenem, meropenem	NA	Colistin	Aztreonam, ceftazidime-avibactam, ceftolozane-tazobactam, cefiderocol, tigecycline, cefepime
<i>Pseudomonas aeruginosa</i>	Cefepime, aztreonam, imipenem, meropenem	NA	Amikacin, ceftazidime-avibactam, ceftolozane-tazobactam, ciprofloxacin, colistin	Cefiderocol, tigecycline

NA = not available

**Table 4 Susceptibility Testing at Each Visit**

Visit	IHMA Organism ID	AMK	AZT	CFPM	CAZ/ AVI	CEF/ TAZ	CPFX	CST	IPM	MEPM	CFDC	TGC
		MIC µg/mL										
Screening/ Baseline	<i>Acinetobacter baumannii</i> E877010	32	> 32	> 16	64	64	> 4	1	32	32	1	2
Screening/ Baseline	<i>Pseudomonas aeruginosa</i> E877009	≤ 4	32	16	8	1	0.5	2	16	16	0.5	> 4

AMK = amikacin; AZT = aztreonam; CAZ/AVI = ceftazidime-avibactam; CEF/TAZ = ceftolozane-tazobactam; CFDC = cefiderocol; CFPM = cefepime; CPFX = ciprofloxacin; CST = colistin; ID = identification; IHMA = International Health Management Associates; IPM = imipenem; MEPM = meropenem; MIC = minimum inhibitory concentration; TGC = tigecycline

**Table 5 Chest Radiograph Results**

Visit	Lung Fields/ Airways	Heart/ Vessels	Other Structures	Comparison of Lung Fields to Screening
Screening/Baseline	Bilateral infiltrates	NA	NA	NA
Early Assessment	Bilateral small infiltrates, minor pleural effusion right lung	NA	NA	Worsened
End of Treatment	Bilateral small infiltrates, minor pleural effusion right lung	NA	NA	Worsened

NA = not applicable

**Table 6 Liver Function Tests**

Visit	AST (RR = 5 to 38)	ALT (RR = 4 to 41)	ALP (RR = 39 to 117)	GGT (RR = 10 to 55)	Total Bilirubin (RR = 0.2 to 1.2)
Screening/Baseline	120 U/L	153 U/L	186 U/L	NA	0.25 mg/dL
Early Assessment	26 U/L	59 U/L	236 U/L	NA	0.26 mg/dL
End of Treatment	28 U/L	27 U/L	401 U/L	287 U/L	0.30 mg/dL

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase;  
GGT = gamma-glutamyl transferase; NA = not applicable; RR = reference range

**Table 7 Renal Function Tests**

Visit	Blood Urea Nitrogen (RR = 20 to 45)	Serum Creatinine (RR = 0.7 to 1.2)	Creatinine Clearance
Screening/Baseline	138.4 mg/dL	2.44 mg/dL	26.90 mL/min
Early Assessment	136.1 mg/dL	1.92 mg/dL	34.18 mL/min
End of Treatment	157.5 mg/dL	3.16 mg/dL	20.77 mL/min

RR = reference range

**Table 8 Coagulation Tests**

Visit	Platelet Count (RR = 140 to 450)	aPTT (RR = 23 to 36)	PT-INR (RR = 0.84 to 1.17)
Screening/Baseline	$366 \times 10^9/L$	27 sec	1.06
Early Assessment	$230 \times 10^9/L$	21.9 sec	1.21
End of Treatment	$120 \times 10^9/L$	NA	NA

aPTT = activated partial thromboplastin time; NA = not available; PT-INR = prothrombin international normalized ratio; RR = reference range

## Subject ID Patient # 24

Subject ID	Patient # 24	Country	Israel			
Age	65	Clinical Diagnosis at Screening	HAP			
Gender	Male	Severity	Moderate			
Race	White	APACHE II Score	26			
Height (cm)	190.0	Causative Pathogen at Screening	Acinetobacter baumannii			
Body Weight (kg)	130.0	CR Evidence at Screening (other than central lab)	Treatment Failure CR-GNB			
MIC of Meropenem	NA	MIC of Cefiderocol	NA			
MIC of Imipenem	NA					
Duration of Study Treatment	14 days	Standard of Care	Tigecycline (100 mg IV), colistin (750,000 U IV)			
Study Drug Treatment	Cefiderocol (1.5 g q12h, 0.75 g q12h IV )					
Microbiological Results at TOC		Day 28 All-cause Mortality	Clinical Outcome at TOC			
Persistence (EOT)		Death (Day 14)	Clinical failure (EOT)			
Medical History (Ongoing)	AF, heavy smoker, COPD, sleep apnea, morbid obesity, chronic lower back pain, polycythemia vera, hypertension, diabetes mellitus, ischemic heart disease, erosive gastritis, congestive heart failure, compressed vertebral fracture D12, adrenal space occupying lesion, stomach ache, leukocytoclastic vasculitis, diffuse ulcers on skin due to vasculitis, leg edema, acute renal failure, steroid therapy, diffuse purpuric rash due to vasculitis, hematuria, high levels of blood LDH, hypoproteinemia, hypoalbuminemia, intermittent high levels of CPK, hyperlactemia, shortness of breath, constipation, mouth petechia, dystrophic nails, low appetite, ST-T changes in V3-6 in ECG, supraventricular tachycardia, candiduria, anemia, melena, hyperphosphatemia, hypermagnesemia, severe leukocytosis, septic shock, hypotension, Enterococcus faecalis bacteremia, Staphylococcus coagulase-negative bacteremia, VRE carrier, enlarged retroperitoneal lymph nodes, left inguinal hernia, intermittent hypocalcemia, mechanical ventilation, mixed respiratory and metabolic acidosis, oliguria, dyslipidemia, prolonged PTT, thrombocytopenia					
Medical History (Not Ongoing)	Hypomagnesemia; pulmonary edema, hyperbilirubinemia, pain in skin lesions, hyponatremia, hyperkalemia, increased amylase, right CVA					
Adverse Event	Day	Severity	Action Taken with Study Drug	Outcome	Causality	Serious
Worsening of blood gases	1	Moderate	NA	Recovered/ resolved	NA	No
Prolonged INR	2	Moderate	Dose not changed	Not recovered/ not resolved	Not related	No
LFT abnormalities	2	Moderate	Dose not changed	Not recovered/no t resolved	Not related	Yes

Secondary infection of skin wound by proteus species	6	Moderate	Dose not changed	Unk	Not related	No
Worsening thrombocytopenia	7	Moderate	Dose not changed	Not recovered/ not resolved	Not related	No
Hyperkalemia	10	Moderate	Dose not changed	Not recovered/ not resolved	Not related	No
Diarrhea	10	Mild	Dose not changed	Recovered/ resolved	Not related	No
Deterioration of <i>Acinetobacter</i> pneumonia	10	Severe	Dose not changed	Fatal	Not related	Yes
Heparin induced thrombocytopenia	12	Moderate	Dose not changed	Not recovered/ not resolved	Not related	No
Pressure sore in back head	13	Mild	Dose not changed	Not recovered/ not resolved	Not related	No
Hypoglycemia	14	Mild	Dose not changed	Not recovered/ not resolved	Not related	No

#### Narrative Summary

A 65-year-old White male from Israel with a history of heavy smoker, COPD, hypertension, ischemic heart disease, AF, polycythemia vera, sleep apnea, diabetes mellitus, morbid obesity, congestive heart failure, was hospitalized (different hospital than study site) on Day -30, due to AF. Apixaban was initiated (for the AF), and then he was discharged home.

He was again hospitalized (to a different hospital than the study site) on Day -18, with a diffuse purpuric rash due to vasculitis, acute renal failure, pulmonary edema and arthralgia. The patient was diagnosed with leukocytoclastic vasculitis. The investigator reported that the leukocytoclastic vasculitis was related to treatment with apixaban, which was subsequently discontinued. He was treated with IV steroids and ceftriaxone.

The patient experienced shortness of breath and hematuria on Day -9. He was transferred to another hospital on Day -9 and then admitted on Day -8 to the study site hospital. It was reported that the patient decided to change hospitals, discharge himself and admitted himself to current facility with severe necrotic skin ulcers and experienced pain in skin lesions. He had a low appetite, anemia and supraventricular tachycardia. He was treated with steroids on Days -8 to -2, ceftriaxone on Days -8 to -3, and ciprofloxacin on Day -8 and Days -5 to -2. He also developed lower GI bleeding (melena) on Day -4 with hyperphosphatemia and hypermagnesemia on Day -3. Severe leukocytosis was reported as well. On Day -2, enlarged retroperitoneal lymph nodes were reported.

On Day -2, he was in septic shock, experienced generalized deterioration, with mixed respiratory and metabolic acidosis, and hypotension. The patient required hemodynamic support, was intubated and attached to mechanical ventilation. He experienced a right CVA, had increased amylase and was transferred to the ICU. The investigator reported that the patient had *E. faecalis* bacteremia, *Staphylococcus* coagulase negative bacteremia, VRE carrier (Day -2). Antibiotic therapy was changed to piperacillin/tazobactam, and colistin was added. TA and blood cultures were obtained on Day -2 and showed *Staphylococcus haemolyticus* (coagulase negative staphylococci.). Urine culture (indwelling catheter) showed *Candida albicans* on Day -2.

CVVHDF was initiated for prevention of fluid overload (Day -2 to Day 10. He was started on

amiodarone (300 mg q6h IV) for the AF (Day -2 to Day 3). On Day -1, the patient had a prolonged PTT. On Day 1, he was assessed for eligibility (for HAP) into the study. Chest x-ray showed infiltrates in the right lower and right middle lobes on Day 1. At Screening, LFTs were in the normal range, and creatinine was raised at 2.47 mg/dL. He was enrolled in the study and was randomized to receive cefiderocol. Ampicillin was added due to *E. faecalis* in the blood culture. Additionally, vancomycin was started for septic shock and amphotericin B due to *C. albicans* found in a urine sample. TA culture show *A. baumannii* growth on Day 2. The unrelated moderate AE of prolonged PT-INR was reported at 4.57. On Day 3 (EA), LFTs were found to be raised, with an AST of 3588 IU/L, ALT of 163 IU/L, LDH of 1329 IU/L, ALP of 331 IU/L, and total bilirubin of 2.4 mg/dL. His WBC count had increased to  $71.05 \times 10^9/L$ , and his creatinine was also raised at 1.55 mg/dL. Clinical outcome was reported as clinical failure. On Day 6, the unrelated moderate AE of secondary infection of skin wound by proteus species was reported. Dose was not changed. The unrelated moderate AE of worsening thrombocytopenia was reported and outcome was reported as not recovered/ not resolved. TA culture collected on Day 9 showed *A. baumannii*. On Day 10, the patient's pneumonia continued to deteriorate. The SAE of deterioration of *Acinetobacter* pneumonia was reported. Dose was not changed. On Day 12, the unrelated moderate AE of heparin-induced thrombocytopenia was reported. The unrelated mild AE of pressure sore in back head was reported on Day 13. On Day 13, cefiderocol dose was reduced to 0.75 g BID due to dialysis. On Day 14 (EOT), the patient completed treatment with cefiderocol. Chest x-ray showed diffuse infiltrates in both lungs. The patient underwent a bronchoscopy. LFTs on this day showed normal ALT and AST, with a raised ALP of 329 IU/L and a raised total bilirubin of 2.11 mg/dL. Microbiological laboratory specimens from the TA and BAL continued to show the pathogen *A. baumannii*. He was considered a clinical failure with microbiological persistence. He had an increase in PT-INR (3.95) and creatinine (2.69 mg/dL), developed severe thrombocytopenia (platelets  $19 \times 10^9/L$ ), and subsequently died on Day 14. The investigator attributed the cause of death to deterioration in *Acinetobacter* pneumonia.

AE = adverse event; AF = atrial fibrillation; ALP = alkaline phosphatase; ALT = alanine aminotransferase; APACHE = Acute Physiology and Chronic Health Evaluation; AST = aspartate aminotransferase; BAL = bronchoalveolar lavage; BID = twice daily; COPD = chronic obstructive pulmonary disease; CPK = creatine phosphokinase; CR = carbapenem resistance; CVA = cerebrovascular accident; CVVHDF = continuous veno-venous hemodiafiltration; EA = Early Assessment; ECG = electrocardiogram; EOT = End of Treatment; GI = gastrointestinal; GNB = Gram-negative bacteria; HAP = hospital-acquired pneumonia; ICU = intensive care unit; ID = identification; INR = international normalized ratio; IV = intravenous; LDH = lactate dehydrogenase; LFTs = liver function tests; MIC = minimum inhibitory concentration; NA = not available; PT-INR = prothrombin international normalized ratio; PTT = partial thromboplastin time; q6h = every 6 hours; q12h = every 12 hours; SAE = serious adverse event; TOC = Test of Cure; TA = tracheal aspirate; unk = unknown; VRE = vancomycin-resistant *Enterococcus*; WBC = white blood cell

**Study Qualifying Diagnosis:** Hospital-acquired pneumonia due to *A. baumannii* was identified with evidence of CR after treatment failure of CR-GNB.

**Study Qualifying Infection History:** A TA sample at EA showed *A. baumannii* resistant to amikacin, ciprofloxacin, imipenem, and meropenem. The isolate was susceptible to colistin (Table 3).

**Current Hospitalization History:** The patient was hospitalized from another hospital for vasculitis and severe necrotic skin ulcers on Day -8, was admitted to the ICU, and was placed into isolation on Day -2. The patient was placed on synchronized intermittent

mandatory ventilation on Day -2 through Day 14. The onset date of the infection was Day -2.

**Clinical Course:** On Day -2, 2 microbiological laboratory specimens were obtained from the TA, and WBC polymorphs (3+,  $\geq 25$ , many) and squamous epithelial cells (1+,  $< 10$ , few) were noted. Gram-negative rods (3+, 4+) were identified. The pathogen *A. baumannii* (semi-quantitation) was identified in each sample. Two microbiological laboratory specimen were also obtained from the blood. The pathogens *E. faecalis* (no quantitation) and *S. haemolyticus* (no quantitation) were identified. A fourth specimen was taken from the urine (indwelling catheter). The pathogen *C. albicans* (quantitation,  $1.0 \times 10^4$ ) was identified.

On Day 1 (Screening/Baseline), the chest x-ray showed infiltrates in the right lower and right middle lobes. Arterial blood gases (ABGs) showed PaO<sub>2</sub> 134 mm Hg, PaCO<sub>2</sub> 62 mm Hg, SaO<sub>2</sub> 95% and FiO<sub>2</sub> 40%. Signs and symptoms at the initial clinical assessment included mild bronchial breath sounds and moderate suctioned respiratory secretions, rales, and dullness on percussion. The Sequential Organ Failure Assessment (SOFA) score was 11, and the Clinical Pulmonary Infection Score (CPIS) was 7 (Table 2). The inflammatory indices of WBC count, C-reactive protein (CRP), and body temperature were  $52.74 \times 10^9/L$ , 167.1 mg/L, and 37.2°C, respectively (Table 1).

Treatment with cefiderocol 1.5 g q12h was initiated on Day 1. He received 23 subsequent infusions of cefiderocol from Day 2 through Day 14. The patient received 3 doses of cefiderocol 0.75 g q 12h on Day 13 through Day 14; the dose was reduced due to dialysis.

On Day 2, he experienced the SAE of moderate LFT abnormalities. Laboratory results from Day 3 included ALT 163 IU/L (reference range [RR] 7 to 45), AST 3588 IU/L (RR 7 to 40), ALP 331 IU/L (RR 45 to 115), and total bilirubin 2.4 mg/dL (RR 0.1 to 1.1). The outcome was not recovered/not resolved. The investigator considered the event not to be related to study medication.

On Day 2, a microbiological laboratory specimen was obtained from the TA, and WBC polymorphs (3+,  $\geq 25$ , many) and squamous epithelial cells (1+,  $< 10$ , few) were noted. Gram-negative rods (2+) were identified. The pathogen *A. baumannii* (no quantitation, heavy growth) was identified.

On Day 3 (EA), the chest x-ray worsened compared with Screening and showed right lower and right middle and left lower lobe infiltrates. ABGs showed PaO<sub>2</sub> 90 mm Hg, PaCO<sub>2</sub> 49 mm Hg, SaO<sub>2</sub> 97% and FiO<sub>2</sub> 50%. Signs and symptoms included mild bronchial breath sounds, moderate dullness on percussion, rales, and suctioned respiratory secretions. The SOFA score was 13, and the CPIS was 7. The inflammatory indices of WBC count, CRP, and body temperature were  $71.05 \times 10^9/L$ , 140.67 mg/L, and 36.5°C, respectively. The clinical outcome was clinical failure.

On Day 5 (Unscheduled Visit), a microbiological laboratory specimen was obtained from the TA, and WBC polymorphs (3+,  $\geq 25$ , many) and squamous epithelial cells (1+,  $< 10$ ,

few) were noted. Gram-negative rods (3+) were identified. The pathogen *A. baumannii* (no quantitation, moderate growth) was identified.

On Day 6 (Unscheduled Visit), a microbiological laboratory specimen was obtained from the TA, and WBC polymorphs (3+,  $\geq 25$ , many) and squamous epithelial cells (1+,  $< 10$ , few) were noted. Gram-negative rods (3+) were identified. The pathogen *A. baumannii* (no quantitation, heavy growth) was identified. A microbiological laboratory specimen was also obtained from the tissue from the wound in the right leg. Gram-negative rods (5+) were identified. The pathogen *Proteus penneri* (no quantitation, heavy growth) was identified.

On Day 9 (Unscheduled Visit), a microbiological laboratory specimen was obtained from the TA, and WBC polymorphs (3+,  $\geq 25$ , many) and squamous epithelial cells (1+,  $< 10$ , few) were noted. Gram-negative rods (2+) were identified. The pathogen *A. baumannii* (no quantitation, heavy growth) was identified.

On Day 10, the patient experienced the SAE of deterioration of *Acinetobacter* pneumonia. The investigator considered the event severe and not related to study medication.

On Day 13 (Unscheduled Visit), a microbiological laboratory specimen was obtained from the TA, and WBC polymorphs (3+,  $\geq 25$ , many) and squamous epithelial cells (1+,  $< 10$ , few) were noted. Gram-negative rods (2+) were identified. The pathogen *A. baumannii* (no quantitation, heavy growth) was identified. The patient was started on dialysis.

On Day 14 (EOT), the patient completed treatment with cefiderocol. Microbiological laboratory specimens were obtained from the TA and BAL, and WBC polymorphs (3+,  $\geq 25$ , many) and squamous epithelial cells (1+,  $< 10$ , few) were noted in the TA. WBC polymorphs (2+, 10 to 24, moderate) were noted in the BAL fluid. Gram-negative rods (2+, 3+) were identified in both cultures, respectively in the TA and BAL. The pathogen *A. baumannii* (no quantitation) was identified in both samples. The chest x-ray worsened compared with Screening and showed diffuse infiltrates in both lungs. ABGs showed PaO<sub>2</sub> 71 mm Hg, PaCO<sub>2</sub> 61 mm Hg, SaO<sub>2</sub> 93%, and FiO<sub>2</sub> 60%. The SOFA score was 15, and the CPIS was 6. The inflammatory indices of WBC count, CRP, and body temperature were  $13.63 \times 10^9/L$ , 187.5 mg/L, and 37.2°C, respectively. He was considered a clinical failure with a microbiological outcome of persistence on the same day that he died, due to the SAE of severe deterioration of *Acinetobacter* pneumonia. He had an increase in PT-INR (3.95) and creatinine (2.69 mg/dL), and developed severe thrombocytopenia (platelets  $19 \times 10^9/L$ ).

**Table 1 Inflammatory Indices**

Visit	White Blood Cell Count (RR = 4 to 10.8)	C-reactive Protein (RR = 0 to 5)	Body Temperature
Screening/Baseline	$52.74 \times 10^9/L$	167.1 mg/L	37.2°C
Early Assessment	$71.05 \times 10^9/L$	140.67 mg/L	36.5°C
End of Treatment	$13.63 \times 10^9/L$	187.5 mg/L	37.2°C

RR = reference range

**Table 2 Sequential Organ Failure Assessment and Total Clinical Pulmonary Infection Score Status**

Visit	SOFA Score	Total CPIS
Screening/Baseline	11	7
Early Assessment	13	7
End of Treatment	15	6

CPIS = Clinical Pulmonary Infection Score; SOFA = Sequential Organ Failure Assessment

**Table 3 Antimicrobial Susceptibility Testing at Screening (European Committee on Antimicrobial Susceptibility Testing)**

Pathogen	Resistant	Intermediate	Susceptible	Not Applicable
<i>Acinetobacter baumannii</i> (Assessment performed at Early Assessment)	Amikacin, ciprofloxacin, imipenem, meropenem	Not applicable	Colistin	Aztreonam, cefepime, ceftazidime- avibactam, ceftolozane- tazobactam, tigecycline

**Table 4 Susceptibility Testing at Each Visit**

Visit	IHMA Organism ID	AMK	AZT	CFPM	CAZ/ AVI	CEF/ TAZ	CPFX	CST	IPM	MEPM	CFDC	TGC
		MIC µg/mL										
Early Assessment	<i>Acinetobacter baumannii</i> Sample ID E736198	> 64	16	> 16	8	4	> 4	2	64	> 64	≤ 0.03	2
Day 6 (Unscheduled)	<i>Proteus penneri</i> Sample ID E736202	≤ 4	2	16	0.5	1	> 4	>8	1	0.25	1	0.5
Day 6 (Unscheduled)	<i>Acinetobacter baumannii</i> Sample ID E736200	> 64	> 32	> 16	64	16	> 4	2	64	64	1	2
Day 9 (Unscheduled)	<i>Acinetobacter baumannii</i> Sample ID E736203	> 64	> 32	> 16	64	32	> 4	2	64	> 64	2	2
Day 13 (Unscheduled)	<i>Acinetobacter baumannii</i> Sample ID E736204	> 64	> 32	> 16	64	16	> 4	2	64	> 64	1	2
End of Treatment	<i>Acinetobacter baumannii</i> Sample ID E736206	> 64	> 32	> 16	64	32	> 4	4	64	> 64	2	2
End of Treatment	<i>Acinetobacter baumannii</i> Sample ID E736205	> 64	> 32	> 16	> 64	32	> 4	4	> 64	64	2	2

AMK = amikacin; AZT = aztreonam; CAZ/AVI = ceftazidime-avibactam; CEF/TAZ = ceftolozane-tazobactam; CFDC = cefiderocol; CFPM = cefepime; CPFX = ciprofloxacin; CST = colistin; ID = identification; IHMA = International Health Management Associates; IPM = imipenem; MEPM = meropenem; MIC = minimum inhibitory concentration; TGC = tigecycline

**Table 5 Chest Radiograph Results**

Visit	Lung Fields/ Airways	Heart/ Vessels	Other Structures	Comparison of Lung Fields to Screening
Screening/Baseline	Infiltrates in right lower and right middle lobes	NA	NA	NA
Early Assessment	Right lower and right middle and left lower lobe infiltrates	NA	NA	Worsened
End of Treatment	Diffuse infiltrates both lungs	NA	NA	Worsened

NA = not applicable

**Table 6 Liver Function Tests**

Visit	AST (RR = 7 to 40)	ALT (RR = 7 to 45)	ALP (RR = 45 to 115)	GGT (RR =10 to 49)	Total Bilirubin (RR = 0.1 to 1.1)
Screening/Baseline	28 IU/L	13 IU/L	108 IU/L	NA	0.83 mg/dL
Early Assessment	3588 IU/L	163 IU/L	331 IU/L	NA	2.4 mg/dL
End of Treatment	29 IU/L	29 IU/L	329 IU/L	177 IU/L	2.11 mg/dL

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase;  
GGT = gamma-glutamyl transferase; NA = Not applicable; RR = reference range

**Table 7 Renal Function Tests**

Visit	Blood Urea Nitrogen	Serum Creatinine (RR = 0.67 to 1.17)	Creatinine Clearance
Screening/Baseline	62 mg/dL	2.47 mg/dL	54.82 mL/min
Early Assessment	29.1 mg/dL	1.55 mg/dL	87.37 mL/min
End of Treatment	65.4 mg/dL	2.69 mg/dL	50.34 mL/min

RR = reference range

**Table 8 Coagulation Tests**

Visit	Platelet Count (RR =130 to 440)	aPTT (RR = 24 to 38)	PT-INR (RR = 0.8 to 1.2)
Screening/Baseline	$78 \times 10^9/L$	64 sec	0.97
Early Assessment	$22 \times 10^9/L$	51 sec	1.24
End of Treatment	$19 \times 10^9/L$	63 sec	3.95

aPTT = activated partial thromboplastin time; PT-INR = prothrombin international normalized ratio;  
RR = reference range

## Subject ID Patient # 25

Subject ID		Patient # 25	Country	Israel		
Age		45	Clinical Diagnosis at Screening	VAP		
Gender		Male	Severity	Severe		
Race		White	APACHE II Score	19		
Height (cm)		188	Causative Pathogen at Screening	Acinetobacter baumannii		
Body Weight (kg)		90	CR Evidence at Screening (other than central lab)	Clinical ETA culture with carbapenem resistance		
MIC of Meropenem		> 64 µg/mL	MIC of Cefiderocol	0.25 µg/mL		
MIC of Imipenem		64 µg/mL				
Duration of Study Treatment		19 days	Standard of Care	Tigecycline (100 mg IV), Meropenem (0.5 g IV)		
Study Drug		Cefiderocol (0.75 g/1.5 g q12h IV)				
Microbiological Results at TOC			Day 28 All-cause Mortality	Clinical Outcome at TOC		
Persistence			Alive (death on Day 39)	Clinical failure		
Medical History (Ongoing)	Psoriasis vulgaris, burn, mechanical ventilation, intermittent high levels of INR, hypoproteinemia, high levels of CRP, hypoalbuminemia, intermittent hypocalcemia, acute respiratory failure, anemia, intermittent high levels of glucose, intermittent high levels of LDH in blood, leukocytosis, intermittent high levels of alkaline phosphatase in blood, tracheostomy, esophagitis, skin graft in hands and legs, pulmonary infiltrate, intermittent high levels of AST, intermittent high levels of ALT, sacral pressure sore, post burn pain, agitation, fluid overload, gluteal hematoma, intermittent low levels of magnesium in blood, intermittent hyperphosphatemia, low blood pressure, intermittent high levels of blood globulin, acute renal failure, respiratory acidosis, hemodialysis					
Medical History (Not Ongoing)	Smoker, hypercholesterolemia, immunocompromised due to inhibitor of tumor necrosis factor alpha (Humira), atrial fibrillation, smoke inhalation, chemosis of eye, pneumococcal pneumonia, enzymatic burn debridement both hands, high levels of CPK in blood, debridement of burns hands and legs, Enterobacter cloacae pneumonia, Klebsiella oxytoca bacteremia, Pseudomonas pneumonia, extravasation of blood from femoral line					
Adverse Event	Day	Severity	Action Taken with Study Drug	Outcome	Causality	Serious
Peripheral edema	3	Moderate	Dose not changed	Not recovered/ not resolved	Not related	No
Pleural effusion	3	Moderate	Dose not changed	Not recovered/ not resolved	Not related	No
Acinetobacter baumannii line infection	9	Moderate	Dose not changed	Recovered/ resolved	Not related	No
Desaturation	10	Moderate	Dose not changed	Recovered/ resolved	Not related	No

Enlarged liver	12	Mild	Dose not changed	Not recovered/ not resolved	Not related	No
Increased bilirubin	13	Moderate	Dose not changed	Not recovered/ not resolved	Not related	No
<i>Pseudomonas</i> growth in ETA	15	Moderate	Dose not changed	Not recovered/ not resolved	Not related	No
Abnormal liver chemistry criteria	18	Moderate	Dose not changed	Not recovered/ not resolved	Not related	Yes
Deterioration of increased bilirubin blood levels	18	Severe	Dose not changed	Not recovered/ not resolved	Not related	No
High levels of SGOT/AST	18	Moderate	Drug withdrawn	Recovered/ resolved	Not related	No
High levels of SGPT/ALT	18	Moderate	Drug withdrawn	Not recovered/ not resolved	Not related	No
Coffee ground	23	Mild	NA	Recovered/ resolved	Not related	No
Intermittent high levels of lactate	24	Moderate	NA	Not recovered/ not resolved	Not related	No
Serotic secretion from the skin	25	Moderate	NA	Not recovered/ not resolved	Not related	No
Thrombocytopenia	28	Moderate	NA	Not recovered/ not resolved	Not related	No
Bacteriuria <i>A. baumannii</i>	29	Mild	NA	Not recovered/ not resolved	Not related	No
Pressure sore in the left ear	32	Mild	NA	Not recovered/ not resolved	Not related	No
Candidemia– <i>Candida glabrata</i>	35	Mild	NA	Recovered/ resolved	Not related	No
<i>Acinetobacter baumannii</i> and <i>Proteus mirabilis</i> in tip of dialysis catheter	35	Moderate	NA	Not recovered/ not resolved	Not related	No
Ascites	36	Moderate	NA	Not recovered/ not resolved	Not related	No

Metabolic acidosis	36	Severe	NA	Not recovered/ not resolved	Not related	No
Bacteremia- <i>P. mirabilis</i>	36	Moderate	NA	Not recovered/ not resolved	Not related	No
Bacteriuria- <i>P. mirabilis</i>	36	Mild	NA	Not recovered/ not resolved	Not related	No
Deterioration of respiratory acidosis	36	Severe	NA	Not recovered/ Not resolved	Not related	No
Respiratory deterioration	36	Severe	NA	Not recovered/ not resolved	Not related	No
Edematous pancreas per CT	36	Moderate	NA	Not recovered/ not resolved	Not related	No
Thickening of intestinal loops per CT	36	Moderate	NA	Not recovered/ not resolved	Not related	No
Tracheal damage	36	Mild	NA	Recovered/ resolved	Not related	No
Supra- ventricular tachycardia	37	Severe	NA	Recovered/ resolved	Not related	No
Septic shock	38	Severe	NA	Fatal	Not related	Yes

#### Narrative Summary

A 45-year-old white male from Israel had a medical history of smoking, psoriasis vulgaris, and AF. On Day -42, the patient had severe burns from a Molotov cocktail (petrol bomb). He had severe burns on face and body (56%) with smoke inhalation. The patient was intubated, started on SIMV on Day -42, and admitted on Day -41. He was transferred to another ICU hospital on Day -40 where he was again intubated due to acute respiratory failure and placed on mechanical ventilation with NO with high jet ventilation. He underwent repeated bronchoscopies to extract soot from the lungs. Due to consolidation and growth of *Streptococcus pneumoniae* found in the TA, he was treated with ceftriaxone and then piperacillin-tazobactam. Pneumococcal pneumonia was reported on Day -40 and treated with meropenem. Vancomycin was provided for one day. On Day -31, the patient underwent a tracheostomy, was transferred to the burn unit (Day -30), and the antibiotic (not specified) was stopped. Amiodarone was started for AF (Day -29 to Day 2). On Day -18, *E. cloacae* was reported. On Day -17, he developed *K. oxytoca* bacteremia.

On Day -16, TA culture showed *E. cloacae*, and treatment was provided with meropenem 1 g q8h. On Day -11, carbapenem resistant *Pseudomonas* grew in the TA and *Pseudomonas* pneumonia was reported; treatment was changed to ceftazidime (Day -9 to Day -2) and ciprofloxacin (Day -9 to Day -1, Day 19 to Day 20, and Day 22 onwards). On Day -9, he developed anemia which was attributed to a gluteal hematoma related to a femoral line extravasation and treated with packed red blood cells. Low blood pressure was reported on Day -7.

On Day -4, the patient was in renal failure, which was attributed to contrast media, NSAIDs, bleeding, and sepsis (creatinine increased 4.7). TA from Day -4 to Day -2 showed MDR *A. baumannii*, and on Day -1, he was treated with tigecycline and meropenem. On Day -1, consolidation in both lungs was reported with deterioration of respiratory parameters; PEEP and FiO<sub>2</sub> were increased. He was started on hemodialysis.

On Day 1, TA culture showed *A. baumannii*. The patient was evaluated for CREDIBLE-CR study eligibility and was enrolled with a diagnosis of VAP. Clinical assessment showed moderate suctioned respiratory secretions, rales, rhonchi, and dullness on percussion. The WBC count was high, with high ALP and LDH. Chest x-ray showed diffuse consolidations in both lungs. He was randomized and given cefiderocol 0.75g q12h, based on renal function.

On Day 3 (EA), chest x-ray showed diffuse infiltrates. TA culture showed *A. baumannii*. Pleural fluid was cultured and found to be negative. Clinical outcome showed clinical failure. The moderate unrelated AE of pleural effusion was reported. Right chest tube was inserted on Day 4 as treatment for pleural effusion and CVVHDF was provided (Day 12) for acute renal failure. The TA and tip of the right axillary arterial line cultures showed *A. baumannii* on Day 9. Results from TA culture on Day 14 showed *A. baumannii* and *Pseudomonas aeruginosa*. The moderate unrelated AE of desaturation was reported on Day 10 and outcome of the AE was recovered/resolved on the same date. The moderate unrelated AE of *A. baumannii* line infection was reported and the outcome of the AE was recovered/resolved on Day 14. The moderate unrelated AE of *Pseudomonas* growth in ETA was reported on Day 15.

On Day 18, the moderate, unrelated SAE of abnormal liver chemistry criteria was reported. The moderate unrelated AEs of high levels of SGOT/AST and SGPT/ALT were both reported. Study drug was withdrawn due to both events and the outcome was reported as recovered/resolved for the AE of high levels of SGLT/AST.

On Day 19 (EOT), cefiderocol treatment was discontinued with clinical failure and microbiological persistence. Clinical assessment showed moderate suctioned respiratory secretions, rales, rhonchi, and dullness on percussion. The WBC count was elevated and chest x-ray showed diffuse infiltrates with improved pleural effusion. The TA culture was positive for *A. baumannii* and *P. aeruginosa*. After stopping cefiderocol on Day 19, the patient was given colistin on Day 19 and tigecycline from Day 20 until Day 38. Meropenem and ceftazidime were also provided. At this visit, the following labs were all elevated: AST 129 IU/L, ALT 176 IU/L, ALP 1233 IU/L, GGT 1956 IU/L and TBL 11.94 mg/dL.

On Day 20, tazocin was provided for one day and ceftazidime was given for 3 days. Blood labs showed increased AST at 175 IU/L on Day 21. On Day 22, vancomycin was provided.

On Day 26, the TA culture showed *A. baumannii*. Clinical/microbiological outcomes were reported as clinical failure and persistence, respectively. WBC count was elevated with TBL at 28.68 mg/dL; liver enzyme remained elevated. Chest x-ray showed improvement of infiltrates on right base.

On Day 33, clinical/microbiological outcomes reported as clinical failure and persistence, respectively. WBC blood count was high and elevated liver enzymes continued to decrease with the exception of AST; chest-x-ray showed improvement of infiltrates. The mild, unrelated AE, growth of *Candida glabrata* in blood was reported on Day 35, and outcome was recovered/resolved on Day 36. On Day 35, the moderate unrelated AE of *A. baumannii* and *P. mirabilis* in tip of dialysis catheter was reported.

On Day 36, the patient's condition deteriorated; BAL culture grew *A. baumannii* and *P. aeruginosa*. Blood, urine, and respiratory samples grew *P. mirabilis*. Vancomycin and amphotericin B were administered. The patient developed septic shock (severe) on Day 38, which led to death on Day 39 (20 days after stopping cefiderocol). The event of septic shock was considered by the investigator to be not to be related to study drug and no further information was provided.

AE = adverse event; AF = atrial fibrillation; ALP = alkaline phosphatase; ALT = alanine aminotransferase; APACHE = Acute Physiology and Chronic Health Evaluation; AST = aspartate aminotransferase; BAL = bronchoalveolar lavage; CPK = creatine phosphokinase; CPE = carbapenemase-producing *Enterobacteriaceae*; CR = carbapenem resistance; CRP = C-reactive protein; CT = computed tomography; CVVHDF = continuous venovenous hemodiafiltration; EA = Early Assessment; EOT = End of Treatment; ETA = endotracheal aspirate; GGT = gamma-glutamyl transferase; ICU = intensive care unit; ID = identification; INR = international normalized ratio; IV = intravenous; LDH = lactate dehydrogenase; MIC = minimum inhibitory concentration; NA = not available; NO = nitric oxide; NSAID = non-steroidal anti-inflammatory drug; PEEP = positive end-expiratory pressure; q8h = every 8 hours; q12h = every 12 hours; SAE = serious adverse event; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; SIMV = synchronized intermittent mandatory ventilation; TA = tracheal aspirate; TBL = total bilirubin; TOC = Test of Cure; unk = unknown; VAP = ventilator-associated pneumonia; WBC = white blood cell

**Study qualifying diagnosis:** Ventilator-associated pneumonia due to *A. baumannii* was identified with evidence of CR through a clinical endotracheal aspirate culture with carbapenem resistance.

**Study qualifying infection history:** On Day -2, a sample obtained from the TA sample showed *A. baumannii* resistant to amikacin, ciprofloxacin, imipenem, and meropenem (Table 3). The isolate was susceptible to colistin.

**Current hospitalization history:** The patient was hospitalized on Day -41 from an acute care treatment center as an urgent admission due to burns and was placed into the ICU; SIMV was started on Day -42 and continued through Day 39. The onset date of the infection was on Day -1.

**Clinical course:** On Day -2, a microbiological laboratory specimen was obtained from the tracheal aspirate. WBC polymorphs (1+, < 10, few) and squamous epithelial cells (1+, < 10, few) were noted. Gram-negative rods (2+) were identified. The pathogen *A. baumannii* (no quantitation, heavy growth) was identified.

On Day 1 (Screening/Baseline), a microbiological laboratory specimen was obtained from the TA, and WBC polymorphs (1+, < 10, few) and squamous epithelial cells (1+, < 10, few) were noted. Gram-negative rods (2+) were identified. The pathogen *A. baumannii* (no quantitation, heavy growth) was identified. A chest radiograph showed diffuse consolidations in both lungs (Table 5). The patient was on a ventilator; and arterial blood gases (ABGs) showed PaO<sub>2</sub> at 83 mm Hg, PaCO<sub>2</sub> at 57 mm Hg, SaO<sub>2</sub> at 94%, FiO<sub>2</sub> at 60%, PEEP at 10 cm H<sub>2</sub>O, and pressure support at 16 cm H<sub>2</sub>O. The initial clinical assessment of signs and symptoms showed moderate suctioned respiratory secretions, rales, rhonchi, and dullness on percussion. The Sequential Organ Failure Assessment (SOFA) score was 6, and the total Clinical Pulmonary Infection Score (CPIS) was 6 (Table 2). The inflammatory indices of WBC count, CRP, and body temperature were  $21.28 \times 10^9/L$ , 230.4 mg/L, and 37.3°C, respectively (Table 1).

The patient received his first dose of cefiderocol (0.75g q12h IV) on Day 1 and received 38 subsequent doses of cefiderocol (0.75 to 1.5 g, q12h, IV) through Day 19. The dose of cefiderocol was adjusted due to renal function.

On Day 3 (EA), a microbiological laboratory specimen was obtained from the TA, and WBC polymorphs (1+, < 10, few) and squamous epithelial cells (1+, < 10, few) were noted. Gram-negative rods (2+) were identified. The pathogen *A. baumannii* (no quantitation, heavy growth) was identified. Pleural fluid was cultured and found to be negative. A microbiological laboratory specimen was obtained from the blood. Gram-negative rods (2+) were identified. The contaminate *Staphylococcus epidermidis* (no quantitation) was identified. A chest radiograph showed diffuse infiltrates and no change in the lung fields compared to Screening. The patient was on a ventilator; ABGs showed PaO<sub>2</sub> at 173 mm Hg, PaCO<sub>2</sub> at 58 mm Hg, SaO<sub>2</sub> at 99%, and FiO<sub>2</sub> at 70%. Signs and symptoms included moderate suctioned respiratory secretions, rales, rhonchi, and dullness on percussion. The SOFA score was 8, and the total CPIS was 6. The inflammatory indices of WBC count, CRP, and body temperature were  $19.31 \times 10^9/L$ , 195 mg/L, and 37.6°C, respectively. Clinical outcome showed clinical failure.

On Day 3, the patient experienced the AE of peripheral edema. The patient did not recover from the event. The investigator considered the event moderate and not related to study medication.

On Day 5, a microbiological laboratory sample was obtained from the TA, and WBC polymorphs (1+, < 10, few) and squamous epithelial cells (1+, < 10, few) were noted. Gram-negative rods (2+) were identified. The pathogen *A. baumannii* (no quantitation, heavy growth) was identified.

On Day 6, a microbiological laboratory sample was obtained from the TA, and WBC polymorphs (1+, < 10, few) and squamous epithelial cells (1+, < 10, few) were noted. Gram-negative rods (2+) were identified. The pathogen *A. baumannii* (no quantitation, heavy growth) was identified.

On Day 8, a microbiological laboratory sample was obtained from the TA, and WBC polymorphs (1+, < 10, few) and squamous epithelial cells (1+, < 10, few) were noted. Gram-negative rods (2+) were identified. The pathogen *A. baumannii* (no quantitation, heavy growth) was identified.

On Day 9, the patient experienced the AE of *A. baumannii* line infection. The patient recovered from the event. The investigator considered the event moderate and not related to study medication. A microbiological laboratory sample was obtained from the tip of the axillary arterial line (right). The pathogen *A. baumannii* (quantitation,  $> 1.0 \times 10^5$ ) was identified.

On Day 12, cefiderocol was increased to 1.5 g q12h based on renal function.

On Day 13, the patient experienced the AE of increased bilirubin. Treatment included ursodeoxycholic acid. The patient did not recover from the event. The investigator considered the event moderate and not related to study medication.

On Day 14, a microbiological laboratory specimen was obtained from the TA, and WBC polymorphs (1+, < 10, few) and squamous epithelial cells (1+, < 10, few) were noted. Gram-negative rods (+) were identified. The pathogens *A. baumannii* (no

quantitation, heavy growth) and *P. aeruginosa* (no quantitation, heavy growth) were identified. A chest radiograph showed diffuse infiltrates and no change in the lung fields compared to Screening. The patient was on a ventilator; ABGs showed PaO<sub>2</sub> at 144 mm Hg, PaCO<sub>2</sub> at 36 mm Hg, SaO<sub>2</sub> at 99%, and FiO<sub>2</sub> at 45%. Signs and symptoms included moderate suctioned respiratory secretions, rales, rhonchi, and dullness on percussion. The SOFA score was 8, and the total CPIS was 4. The inflammatory indices of WBC count, CRP, and body temperature were  $18.84 \times 10^9/L$ , 355.25 mg/L, and 37.9°C, respectively.

On Day 15, the patient experienced the AE of *Pseudomonas* growth in ETA. Treatment included meropenem, ciprofloxacin, tigecycline, and coliracin. The patient did not recover from the event. The investigator considered the event moderate and not related to study medication. A microbiological laboratory specimen was obtained from the TA, and WBC polymorphs (1+, < 10, few) and squamous epithelial cells (1+, < 10, few) were noted. Gram-negative rods (2+) were noted. The pathogens *A. baumannii* (no quantitation, heavy growth) and *P. aeruginosa* (no quantitation, heavy growth) were noted.

On Day 18, the patient experienced the SAE of moderate abnormal liver chemistry criteria. The patient did not recover from the event. The investigator considered the event not related to study drug.

On Day 19, a microbiological laboratory specimen was obtained from the TA, and WBC polymorphs (3+,  $\geq 25$ , many) and squamous epithelial cells (1+, < 10, few) were noted. Gram-negative rods (6+) were identified. The pathogens *A. baumannii* (no quantitation, heavy growth) and *P. aeruginosa* (no quantitation, heavy growth) were identified. A chest radiograph showed diffuse consolidations in both lungs and improved pleural effusion, and the lung fields compared to Screening had worsened. The patient was on a ventilator; ABGs showed PaO<sub>2</sub> at 136 mm Hg, PaCO<sub>2</sub> at 48 mm Hg, SaO<sub>2</sub> at 98%, and FiO<sub>2</sub> at 45%. Signs and symptoms included moderate suctioned respiratory secretions, rales, rhonchi, and dullness on percussion. The SOFA score was 10, and the total CPIS was 5. The inflammatory indices of WBC count, CRP, and body temperature were  $16.76 \times 10^9/L$ , 267.53 mg/L, and 38.4°C, respectively. Clinical/microbiological outcomes were reported as clinical failure and persistence, respectively.

On Day 20, a microbiological laboratory specimen was obtained from the TA, and WBC polymorphs (1+, < 10, few) and squamous epithelial cells (1+, < 10, few) were noted. Gram-negative rods (6+) were identified. The pathogen *A. baumannii* (no quantitation, heavy growth) was identified.

On Day 22, a microbiological laboratory specimen was obtained from the TA, and WBC polymorphs (3+,  $\geq 25$ , many) were noted. Gram-negative rods (4+) were identified. The pathogens *A. baumannii* (no quantitation, heavy growth) and *P. aeruginosa* (no quantitation, heavy growth) were identified.

On Day 26, a microbiological laboratory specimen was obtained from the TA, and WBC polymorphs (1+, < 10, few) and squamous epithelial cells (1+, < 10, few) were noted.

Gram-negative rods (+) were identified. The pathogen *A. baumannii* (no quantitation, heavy growth) was identified. A chest radiograph showed improvement of infiltrates still on right base, and the lung fields compared to Screening were improved. The patient was on a ventilator; ABGs showed PaO<sub>2</sub> at 133 mm Hg, PaCO<sub>2</sub> at 38 mm Hg, SaO<sub>2</sub> at 99%, and FiO<sub>2</sub> at 40%. Signs and symptoms included moderate suctioned respiratory secretions, rales, rhonchi, and dullness on percussion. The SOFA score was 9, and the total CPIS was 4. The inflammatory indices of WBC count, CRP, and body temperature were  $21.45 \times 10^9/L$ , 217 mg/L, and 37.9°C, respectively. Clinical/microbiological outcomes were reported as clinical failure and persistence, respectively.

On Day 29, a microbiological laboratory specimen was obtained from the tracheal aspirate, and WBC polymorphs (1+, < 10, few) and squamous epithelial cells (1+, < 10, few) were noted. Gram-negative rods (6+) were identified. The pathogen *A. baumannii* (no quantitation, heavy growth) was identified. Another microbiological laboratory sample was obtained from the urine via an indwelling catheter. The pathogen *A. baumannii* (quantitation,  $> 1 \times 10^5$ ) was identified.

On Day 33, the chest radiograph showed improvement of infiltrates and improvement in lung fields in comparison to Screening. The patient was on a ventilator; ABGs showed PaO<sub>2</sub> at 138 mm Hg, PaCO<sub>2</sub> at 35 mm Hg, SaO<sub>2</sub> at 99%, and FiO<sub>2</sub> at 30%. Signs and symptoms included moderate suctioned respiratory secretions, rales, rhonchi, and dullness on percussion. The SOFA score was 12, and the total CPIS was 5. The inflammatory indices of WBC count, CRP, and body temperature were  $21.78 \times 10^9/L$ , 85.6 mg/L, and 37.7°C, respectively. The patient was considered a clinical failure with microbiological persistence.

On Day 35, 2 microbiological laboratory specimens were obtained from the TA and WBC polymorphs (1+, < 10, few) and squamous epithelial cells (1+, < 10, few) were noted in both specimens. Gram-negative rods (+) were identified in both specimens. The pathogens *A. baumannii* (no quantitation, heavy growth) and *P. aeruginosa* (no quantitation, heavy growth) were identified in both specimens. An additional microbiological laboratory specimen was obtained from the urine via an indwelling catheter. The pathogens *A. baumannii* (no quantitation, heavy growth) *P. aeruginosa* (no quantitation, heavy growth) were identified. An additional microbiological laboratory specimen was obtained from the dialysis catheter tip. The pathogens *P. mirabilis* (quantitation,  $> 1.5 \times 10^1$ ) and *A. baumannii* (quantitation,  $> 1.5 \times 10^1$ ) were identified. The patient experienced the AE of growth of *Candida glabrata* in the blood. Treatment included amphotericin B (90 mg, IV, every 24 hours). The patient recovered from the event. The investigator considered the event mild and not related to the study medication.

On Day 36 (Unscheduled Visit), microbiological laboratory specimen was obtained from the blood. The pathogen *P. mirabilis* was identified. An additional microbiological laboratory specimen was obtained from the BAL fluid, and WBC polymorphs (1+, < 10, few) and squamous epithelial cells (1+, < 10, few) were noted. Gram-negative rods (2+) were identified. The pathogens *P. aeruginosa* (no quantitation, heavy growth) and *A. baumannii* (no quantitation, heavy growth) were identified.

On Day 36, the patient experienced the AEs of severe deterioration of respiratory acidosis, moderate edematous pancreas per CT, moderate thickening of intestinal loops per CT, and mild tracheal damage. Treatment included tranexamic acid. The patient did not recover from the events. The following day on Day 37, the patient experienced the AE of supraventricular tachycardia. Treatment included cardioversion. The patient recovered from the tracheal damage and supraventricular tachycardia. The investigator considered the events not related to study medication.

On Day 38 (End of Study), the patient experienced the SAE of septic shock. The outcome was Fatal. The investigator considered the event severe and not related to the study medication. The patient died on Day 39 due to the SAE of severe septic shock, 20 days after receiving his last dose of study medication.

**Table 1 Inflammatory Indices**

Visit	White Blood Cell Count (RR = 4 to 10.8)	C-reactive Protein (RR = 0 to 5)	Body Temperature
Screening/Baseline	$21.28 \times 10^9/L$	230.4 mg/L	37.3°C
Early Assessment	$19.31 \times 10^9/L$	195 mg/L	37.6°C
Day 14	$18.84 \times 10^9/L$	355.25 mg/L	37.9°C
End of Treatment	$16.76 \times 10^9/L$	267.53 mg/L	38.4°C
Test of Cure	$21.45 \times 10^9/L$	217 mg/L	37.9°C
Follow-up	$21.78 \times 10^9/L$	85.6 mg/L	37.7°C

RR = reference range

**Table 2 Sequential Organ Failure Assessment and Total Clinical Pulmonary Infection Score Status**

Visit	SOFA Score	Total CPIS
Screening/Baseline	6	6
Early Assessment	8	6
Day 14	8	4
End of Treatment	10	5
Test of Cure	9	4
Follow-up	12	5

CPIS = Clinical Pulmonary Infection Score; SOFA = Sequential Organ Failure Assessment

**Table 3 Antimicrobial Susceptibility Testing at Screening (European Committee on Antimicrobial Susceptibility Testing)**

Pathogen	Resistant	Intermediate	Susceptible	Not Applicable
<i>Acinetobacter baumannii</i>	Amikacin, ciprofloxacin, imipenem, meropenem	NA	Colistin	Aztreonam, cefepime, ceftazidime-avibactam, ceftolozane-tazobactam, cefiderocol, tigecycline

NA = not applicable

**Table 4 Susceptibility Testing at Each Visit**

Visit	IHMA Organism ID	AMK	AZT	CFPM	CAZ/ AVI	CEF/ TAZ	CPFX	CST	IPM	MEPM	CFDC	TGC
		MIC µg/mL										
Screening/ Baseline	<i>Acinetobacter baumannii</i> Sample ID E736188	> 64	32	> 16	64	32	> 4	1	64	> 64	0.25	2
Early Assessment	<i>Acinetobacter baumannii</i> Sample ID E736189	> 64	> 32	> 16	64	32	> 4	1	64	64	0.5	4
Unscheduled Visit Day 5	<i>Acinetobacter baumannii</i> Sample ID E736194	> 64	> 32	> 16	64	32	> 4	2	64	64	0.5	2
Unscheduled Visit Day 6	<i>Acinetobacter baumannii</i> Sample ID E736191	> 64	> 32	> 16	64	32	> 4	1	64	64	0.5	1
Unscheduled Visit Day 8	<i>Acinetobacter baumannii</i> Sample ID E736190	> 64	32	> 16	64	32	> 4	1	64	64	2	2
Unscheduled Visit Day 9	<i>Acinetobacter baumannii</i> Sample ID E736192	≤ 4	32	> 16	> 64	32	> 4	1	> 64	> 64	1	2
Day 14	<i>Pseudomonas aeruginosa</i> Sample ID E736193	≤ 4	32	4	4	0.5	0.5	2	16	16	1	> 4
Day 14	<i>Acinetobacter baumannii</i> Sample ID E736195	> 64	> 32	> 16	> 64	> 64	> 4	2	64	> 64	4	1

Visit	IHMA Organism ID	AMK	AZT	CFPM	CAZ/ AVI	CEF/ TAZ	CPFX	CST	IPM	MEPM	CFDC	TGC
		MIC µg/mL										
Unscheduled Visit Day 15	<i>Pseudo- monas aeruginosa</i> Sample ID E851032	≤4	32	4	4	0.5	≤ 0.25	2	8	16	0.5	4
Unscheduled Visit Day 15	<i>A. baumannii</i> Sample ID E851033	> 64	> 32	>16	> 64	> 64	> 4	1	64	> 64	2	1
End of Treatment	<i>Acinetobacter baumannii</i> Sample ID E851034	> 64	> 32	> 16	> 64	> 64	> 4	1	64	> 64	2	2
End of Treatment	<i>Pseudomonas aeruginosa</i> Sample ID E851035	≤ 4	16	8	8	0.5	0.5	2	8	16	0.25	> 4
Test of Cure	<i>Acinetobacter baumannii</i> Sample ID E590509	> 64	> 32	> 16	> 64	> 64	> 4	1	> 64	> 64	2	2
Follow-up	<i>Acinetobacter baumannii</i> Sample ID E590516	> 64	32	> 16	> 64	> 64	> 4	1	> 64	> 64	2	2
Follow-up	<i>Pseudomonas aeruginosa</i> Sample ID E590517	≤ 4	16	4	4	0.5	> 4	2	8	8	0.12	> 4
Follow-up	<i>Proteus mirabilis</i> Sample ID 851021	≤ 4	≤ 0.5	≤ 0.5	0.12	0.5	> 4	> 8	1	≤ 0.03	0.12	1

AMK = amikacin; AZT = aztreonam; CAZ/AVI = ceftazidime-avibactam; CEF/TAZ = ceftolozane-tazobactam; CFDC = cefiderocol; CFPM = cefepime;  
CPFX = ciprofloxacin; CST = colistin; ID = identification; IHMA = International Health Management Associates; IPM = imipenem; MEPM = meropenem; MIC = minimum  
inhibitory concentration; TGC = tigecycline

**Table 5 Chest Radiograph Results**

Visit	Lung Fields/Airways	Heart/Vessels	Other Structures	Comparison of Lung Fields to Screening
Screening/Baseline	Diffuse consolidations both lungs	No abnormality	None	NA
Early Assessment	Diffuse infiltrates	NA	NA	No change
Day 14	Diffuse infiltrates	NA	NA	No change
End of Treatment	Diffuse consolidations both lungs, improved pleural effusion	NA	NA	Worsened
Test of Cure	Improvement of infiltrates still on right base	NA	NA	Improved
Follow-up	Improvement of infiltrates	NA	NA	Improved

NA = not available

**Table 6 Liver Function Tests**

Visit	AST (RR = 7 to 40)	ALT (RR = 7 to 45)	ALP (RR = 45 to 115)	GGT (RR = 10 to 49)	Total Bilirubin (RR = 0.1 to 1.1)
Screening/Baseline	41 IU/L	31 IU/L	355 IU/L	NA	1.01 mg/dL
Early Assessment	26 IU/L	20 IU/L	292 IU/L	NA	0.82 mg/dL
Day 14	30 IU/L	42 IU/L	604 IU/L	NA	3.21 mg/dL
End of Treatment	129 IU/L	176 IU/L	1233 IU/L	1956 IU/L	11.94 mg/dL
Day 26	175 IU/L	177 IU/L	NA	NA	NA
Test of Cure	49 IU/L	126 IU/L	1350 IU/L	1529 IU/L	28.68 mg/dL
Follow-up	54 IU/L	105 IU/L	754 IU/L	620 IU/L	24.59 mg/dL

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase;  
GGT = gamma-glutamyl transferase; NA = not available; RR = reference range

**Table 7 Renal Function Tests**

Visit	Blood Urea Nitrogen	Serum Creatinine (RR = 0.67 to 1.17)	Creatinine Clearance
Screening/Baseline	50 mg/dL	4.28 mg/dL	27.75 mL/min
Early Assessment	48.3 mg/dL	4.03 mg/dL	29.47 mL/min
Day 14	49.13 mg/dL	1.96 mg/dL	NA
End of Treatment	95.2 mg/dL	1.29 mg/dL	92.05 mL/min
Test of Cure	58.33 mg/dL	1.05 mg/dL	113.10 mL/min
Follow-up	35.93 mg/dL	0.66 mg/dL	179.92 mL/min

NA = not available; RR = reference range

**Table 8**                      **Coagulation Tests**

<b>Visit</b>	<b>Platelet Count (RR = 130 to 440)</b>	<b>aPTT (RR = 24 to 38)</b>	<b>PT-INR (RR = 0.8 to 1.2)</b>
Screening/Baseline	$332 \times 10^9/\text{L}$	29 sec	1.54
Early Assessment	$311 \times 10^9/\text{L}$	30 sec	1.35
Day 14	$362 \times 10^9/\text{L}$	39 sec	1.36
End of Treatment	$377 \times 10^9/\text{L}$	33 sec	1.38
Test of Cure	$212 \times 10^9/\text{L}$	43 sec	1.48
Follow-up	$15 \times 10^9/\text{L}$	71 sec	1.53

aPTT = activated partial thromboplastin time; PT-INR = prothrombin international normalized ratio;  
RR = reference range

## Subject ID Patient # 26

Subject ID	Patient # 26	Country	Israel			
Age	64	Clinical Diagnosis at Screening	VAP			
Gender	Male	Severity	Severe			
Race	White	APACHE II Score	29			
Height (cm)	170.0	Causative Pathogen at Screening	Acinetobacter baumannii			
Body Weight (kg)	82.8	CR Evidence at Screening (other than central lab)	Treatment Failure CR-GNB			
MIC of Meropenem	64 µg/mL	MIC of Cefiderocol	0.25 µg/mL			
MIC of Imipenem	32 µg/mL					
Duration of Study Treatment	4 days	Standard of Care	Colistin (3,000,000 U IV)			
Study Drug Treatment	Cefiderocol (0.75 g q12h IV)					
Microbiological Results at TOC		Day 28 All-cause Mortality		Clinical Outcome at TOC		
Indeterminate		Death (Day 4)		Clinical failure (EA)		
Medical History (Ongoing)	Diabetes mellitus, hyperlipidemia, angina pectoris; cardiac ischemia, peripheral vascular disease, carotid artery occlusion, carotid artery stenosis, hypertension, cerebrovascular disease, anemia, metabolic acidosis, acute renal failure, hemodialysis					
Medical History (Not Ongoing)	Acute myocardial infarction; aortofemoral (one-side) bypass graft, left; femoral-popliteal graft, right; cardiac arrest; bradycardia, cardiac arrest					
Adverse Event	Day	Severity	Action Taken with Study Drug	Outcome	Causality	Serious
Bradycardia	3	Severe	Dose not changed	Recovered/resolved	Not related	No
Septic shock	4	Severe	Drug interrupted	Fatal	Not related	Yes
Narrative Summary						
A 64-year-old white male from Israel had a medical history of diabetes mellitus, acute myocardial infarction, hyperlipidemia, angina pectoris, cardiac ischemia, peripheral vascular disease, carotid artery occlusion and stenosis, and cerebrovascular disease.						
The patient was hospitalized on Day-15 from an acute care treatment facility for a left aorto-femoral bypass graft (performed on Day -14) due to intermittent claudication from atherosclerosis. On Day -14, the patient received a blood transfusion (2 units) for anemia.						
On Day -13, the patient underwent surgery, with a right femoro-popliteal graft for a suspected right superficial femoral artery thrombosis. He received cefamezin 1 g IV once as prophylaxis. The patient received a blood transfusion (2 units) on Day -12 for anemia.						
On Day -12, the patient experienced cardiac arrest, developed metabolic acidosis, was placed on mechanical ventilation which remained in place until Day -3 , and was transferred to the ICU and cefamezin 1 g IV q8h was initiated again for prophylaxis (stopped Day -5).						
On Day -11, he underwent a right fasciotomy. He was in acute renal failure and was started on hemodialysis (postoperative renal failure). On Day -7, the patient was in bradycardia which deteriorated to a cardiac arrest requiring cardiopulmonary resuscitation.						
On Day -3, sputum culture obtained identified A. baumannii. On Day -1, he received piperacillin-tazobactam and colistin for less than 24 hours. Chest x-ray showed pulmonary congestion.						

hypostasis, an acute upper respiratory tract infection, and a new left sided pleural effusion.

On Day 1, he was assessed for eligibility (VAP) into the study. He was enrolled in the study and was randomized to receive cefiderocol (0.75 g q12h). A blood culture (taken on Day -1) grew *Klebsiella oxytoca*. Sputum samples taken on Day 1 continued to grow *A. baumannii* on culture. The WBC count (blood) was at  $35.10 \times 10^9/L$ . Further Screening laboratory tests showed low hemoglobin of 8 g/dL. He also had raised creatinine, CRP, alkaline phosphatase, total bilirubin of 4.20 mg/dL, and GGT of 289 U/L.

On Day 2, the patient had a tracheostomy. The patient also received a blood transfusion (1 unit) for anemia.

On Day 3, EA, wound swab culture was taken from the left leg and showed a growth of *A. baumannii*. Laboratory tests showed a reduced platelet count of  $56 \times 10^9/L$ , raised CRP, WBC count, ALT, AST, and CPK. He experienced the unrelated severe AE of bradycardia, which was treated with atropine and adrenaline and the AE of bradycardia resolved on the same day (Day 3). The patient was considered to have had clinical failure.

On Day 4, the unrelated SAE of severe septic shock was reported. Study drug was interrupted. He was hemodynamically unstable, anuric, and expired at 6:50 hours. The investigator reported that the patient expired 50 minutes after the start of infusion of the sixth dose of study drug.

AE = adverse event; ALT = alanine aminotransferase; APACHE = Acute Physiology and Chronic Health Evaluation; AST = aspartate aminotransferase; CPK = creatine phosphokinase; CR = carbapenem resistance; CRP = C-reactive protein; EA = Early Assessment; GGT = gamma-glutamyl transferase; GNB = Gram-negative bacteria; ICU = intensive care unit; ID = identification; IV = intravenous; MIC = minimum inhibitory concentration; q8h = every 8 hours; q12h = every 12 hours; SAE = serious adverse event; TOC = Test of Cure; VAP = ventilator-associated pneumonia; WBC = white blood cell

**Study qualifying diagnosis:** Ventilator-associated pneumonia due to *A. baumannii* was identified with evidence of carbapenem resistance through treatment failure CR-GNB.

**Study qualifying infection history:** At the Screening/Baseline visit, a sputum sample showed *A. baumannii* resistant to ciprofloxacin, imipenem, and meropenem. The isolate was susceptible to colistin and had intermediate sensitivity to amikacin (Table 3).

**Current hospitalization history:** The patient was hospitalized on Day -15 from an acute care treatment facility as an elective admission due to a left femoral-popliteal graft due to atherosclerosis of native arteries of extremities onto a general ward. The patient was transferred to the ICU on Day -12 and remained there until his death on Day 4. Synchronized intermittent mandatory ventilation (SIMV) was initiated on Day -12 and continued until the time of death. The onset date of the infection was Day -2.

**Clinical course:** On Day -14, arterial blood gases (ABGs) indicated a PaO<sub>2</sub> of 173 mm Hg, PaCO<sub>2</sub> of 36 mm Hg, SaO<sub>2</sub> 99%, and FiO<sub>2</sub> 40%.

On Day -3, a microbiological laboratory specimen was obtained from the sputum. Gram-negative rods were not identified. The pathogen *A. baumannii* was identified.

On Day -1, a microbiological laboratory specimen was obtained from the blood. Gram-negative rods were not identified. The pathogen *K. oxytoca* was identified.

On Day 1 ( Screening/Baseline), a microbiological laboratory specimen was obtained from the sputum. Gram-negative rods were not identified. The pathogen *A. baumannii* was identified. The chest radiograph showed pulmonary congestion, hypostasis, and acute

upper respiratory infection with new infiltration and left sided pleural effusion. The patient was on a ventilator. The initial clinical assessment of signs and symptoms was performed, and moderate suctioned respiratory secretions, rales and rhonchi were noted. The Sequential Organ Failure Assessment (SOFA) score was 17, and the CPIS was 2 (Table 2). The inflammatory indices of WBC count, CRP, and body temperature were  $35.10 \times 10^9/L$ , 289.8 mg/L, and 38.4°C, respectively (Table 1).

Treatment with cefiderocol (0.75 g q12h) was initiated on Day 1 . He received 5 subsequent infusions of cefiderocol on Days 2 through 4.

On Day 3 ( EA), a microbiological laboratory sample was obtained from a wound of the left leg. Gram-negative rods were not identified. The pathogen *A. baumannii* was identified. A chest radiograph was not performed. He was on a ventilator; the ABGs were PaO<sub>2</sub> 42 mm Hg, PaCO<sub>2</sub> 58 mm Hg, SaO<sub>2</sub> 60%, and FiO<sub>2</sub> 60%. A clinical assessment of signs and symptoms was not performed. The inflammatory indices of WBC, CRP, and body temperature were  $32.40 \times 10^9/L$ , 349.9 mg/L, and 37.3°C, respectively. The patient was considered a clinical failure.

He experienced an AE of severe bradycardia on Day 3. Treatment included atropine (1 mg once IV) and adrenaline (1 mg once IV). The dose of study drug was not changed. The event resolved on the same day. The investigator considered the event not related to study drug.

On Day 4 , the patient experienced an SAE of severe septic shock. Treatment with study drug was interrupted due to the event. The outcome was Fatal, and the patient died 50 minutes after he started receiving the sixth dose of study drug. The vital signs taken prior to the last study drug were systolic blood pressure of 151 mm Hg, diastolic blood pressure of 67 mm Hg, pulse rate of 89 beats per minute, respiratory rate of 18 breaths per minute, and a temperature of 38.2°C. The patient had become hemodynamically unstable, anuric, and developed cardiorespiratory failure. He was treated with high doses of noradrenaline. In addition, he had bradycardia and metabolic acidosis. The investigator considered the event not related to study drug.

**Table 1 Inflammatory Indices**

Visit	White Blood Cell Count (RR = 4 to 10)	C-reactive Protein (RR = 0 to 5)	Body Temperature
Screening/Baseline	$35.10 \times 10^9/L$	289.8 mg/L	38.4°C
Early Assessment	$32.40 \times 10^9/L$	349.9 mg/L	37.3°C

RR = reference range

**Table 2 Sequential Organ Failure Assessment and Total Clinical Pulmonary Infection Score Status**

Visit	SOFA Score	Total CPIS
Screening/Baseline	17	2

CPIS = Clinical Pulmonary Infection Score; SOFA = Sequential Organ Failure Assessment

**Table 3 Antimicrobial Susceptibility Testing at Screening (European Committee on Antimicrobial Susceptibility Testing)**

Pathogen	Resistant	Intermediate	Susceptible	Not Applicable
<i>Acinetobacter baumannii</i>	Ciprofloxacin, imipenem, meropenem	Amikacin	Colistin	Aztreonam, cefepime, ceftazidime-avibactam, ceftolozane-tazobactam, cefiderocol, tigecycline

**Table 4 Susceptibility Testing at Each Visit**

Visit	IHMA Organism ID	AMK	AZT	CFPM	CAZ/ AVI	CEF/ TAZ	CPFX	CST	IPM	MEPM	CFDC	TGC
		MIC µg/mL										
Screening/ Baseline	<i>Acinetobacter baumannii</i> Sample ID E629416	16	> 32	> 16	> 64	16	> 4	1	32	64	0.25	1
Early Assessment	<i>Acinetobacter baumannii</i> Sample ID E629415	16	> 32	> 16	64	32	> 4	2	32	> 64	2	2

AMK = amikacin; AZT = aztreonam; CAZ/AVI = ceftazidime-avibactam; CEF/TAZ = ceftolozane-tazobactam; CFDC = cefiderocol; CFPM = cefepime; CPFX = ciprofloxacin; CST = colistin; ID = identification; IHMA = International Health Management Associates; IPM = imipenem; MEPM = meropenem; MIC = minimum inhibitory concentration; TGC = tigecycline

**Table 5 Chest Radiograph Results**

Visit	Lung Fields/ Airways	Heart/ Vessels	Other Structures	Comparison of Lung Fields to Screening
Screening/ Baseline	Pulmonary congestion, hypostasis, acute upper respiratory infection, new left side pleural effusion	NA	NA	NA

NA = not applicable

**Table 6 Liver Function Tests**

Visit	AST (RR = 0 to 40)	ALT (RR = 10 to 50)	ALP (RR = 40 to 129)	GGT (RR = 8 to 61)	Total Bilirubin (RR = 0.3 to 1.2)
Screening/Baseline	35 U/L	7 U/L	391 U/L	289 U/L	4.20 mg/dL
Early Assessment	946 U/L	143 U/L	472 U/L	162 U/L	4.87 mg/dL

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase;  
GGT = gamma-glutamyl transferase; RR = reference range

**Table 7 Renal Function Tests**

Visit	Blood Urea Nitrogen (RR = 8 to 23)	Serum Creatinine (RR = 0.7 to 1.2)	Creatinine Clearance
Screening/Baseline	60.2 mg/dL	3.95 mg/dL	22.13 mL/min
Early Assessment	72.2 mg/dL	4.92 mg/dL	17.76 mL/min

RR = reference range

**Table 8 Coagulation Tests**

Visit	Platelet Count (RR = 140 to 440)	aPTT (RR = 22 to 32)	PT-INR (RR = 0.75 to 1.3)
Screening/Baseline	$99 \times 10^9/L$	30.4 sec	1.23
Early Assessment	$56 \times 10^9/L$	35.2 sec	1.23

aPTT = activated partial thromboplastin time; NA = not available; PT-INR = prothrombin international normalized ratio; RR = reference range

## Subject ID Patient # 27

Subject ID	Patient # 27	Country	Taiwan			
Age	47	Clinical Diagnosis at Screening	VAP			
Gender	Male	Severity	Severe			
Race	Asian	APACHE II Score	9			
Height (cm)	167.0	Causative Pathogen at Screening	<i>Pseudomonas aeruginosa</i> , <i>Acinetobacter nosocomialis</i> , <i>Stenotrophomonas maltophilia</i> , <i>Chryseobacterium indologenes</i>			
Body Weight (kg)	66.0	CR Evidence at Screening (other than central lab)	Treatment failure CR-GNB (Chromogenic Media)			
MIC of Meropenem	<i>P. aeruginosa</i> , 8 µg/mL; <i>A. nosocomialis</i> , > 64 µg/mL; <i>S. maltophilia</i> , > 64 µg/mL; <i>C. indologenes</i> , > 64 µg/mL	MIC of Cefiderocol	<i>P. aeruginosa</i> , 0.12 µg/mL; <i>A. nosocomialis</i> , 64 µg/mL; <i>S. maltophilia</i> , 0.06 µg/mL; <i>C. indologenes</i> , 0.5 µg/mL			
MIC of Imipenem	<i>P. aeruginosa</i> , 16 µg/mL; <i>A. nosocomialis</i> , 64 µg/mL; <i>S. maltophilia</i> , > 64 µg/mL; <i>C. indologenes</i> , > 64 µg/mL					
Duration of Study Treatment	8 days	Standard of Care	Meropenem (1 g IV) Colistin (4000000 IU IV)			
Study Drug Treatment	Cefiderocol (2 g q8h IV)					
Microbiological Results at TOC		Day 28 All-cause Mortality		Clinical Outcome at TOC		
Persistence (EOT)		Death (Day 8)		Clinical failure (EOT)		
Medical History (Ongoing)	HBV carrier, liver cirrhosis, alcoholism, splenomegaly; bacteremia, ascites; anemia, coagulopathy, metabolic acidosis, thrombocytopenia; spontaneous bacterial peritonitis; upper gastrointestinal bleeding; suspect pleural effusion left, hypokalemia; fungemia, septic shock, hepatic encephalopathy, sinus tachycardia, liver failure, esophageal varicosity bleeding					
Medical History (Not Ongoing)	Conscious disturbance, shortness of breath; PEA s/p CPR, sinus bradycardia					
Adverse Event	Day	Severity	Action Taken with Study Drug	Outcome	Causality	Serious
Massive diarrhea	1	Mild	NA (pre-dose)	Recovered/resolved	NA	No

Worsening liver failure	1	Severe	Dose not changed	Fatal	Not related	Yes
Worsening liver cirrhosis	4	Severe	Dose not changed	Not recovered/ not resolved	Not related	No
Hypotension	5	Severe	Dose not changed	Not recovered/ not resolved	Not related	No
Worsening septic shock	5	Severe	Dose not changed	Fatal	Not related	Yes

#### Narrative Summary

A 47-year-old Asian male with liver cirrhosis was admitted to another hospital on Day -22. He was diagnosed to have anemia, metabolic acidosis, coagulopathy, thrombocytopenia, conscious disturbance, and shortness of breath. He was intubated on the same date.

The patient was diagnosed on admission as having VAP and spontaneous bacterial peritonitis, and was treated with ceftazidime until Day -12 and metronidazole from Day -14 to Day -7. He was also treated with meropenem from Day -12 to Day 1, and tigecycline from Day -7 to Day -4.

On Day -6, the patient was extubated.

On Day -4, the patient developed esophageal varicosity bleeding, and then PEA. Cardiopulmonary resuscitation was performed, and the patient was brought to the study site. The patient was intubated. He was diagnosed as having septic shock.

The patient was treated with tigecycline from Day -2 to Day 1, and colistin from Day -1 to Day 1.

On Day -1, rapid testing of the sputum with chromogenic media was performed, and CR was confirmed.

On Day 1, the patient was enrolled in this study as a patient of VAP. Sputum collected on Day 1 demonstrated *P. aeruginosa*, *C. indologenes*, and *A. nosocomialis* with evidence of carbapenem resistance. *Candida albicans* and *S. maltophilia* were both detected from sputum and considered a pathogen. *Candida parapsilosis* was identified from the blood. He was randomized to the cefiderocol group. Cefiderocol was started on Day 1 and was continued until Day 8. Vancomycin was also started. Fluconazole was given on Day 1, and anidulafungin was administered between Day 1 and Day 7 for the indication of fungemia.

On Day 1, the patient experienced the SAE of severe worsening liver failure. Study drug dose was not changed. Also, the unrelated mild AE of massive diarrhea was reported on Day 1.

On Day 4 (EA), sputum culture was positive and *A. nosocomialis*, *P. aeruginosa*, *S. maltophilia*, and *C. albicans* were identified. The outcome was considered a clinical cure.

On Day 5, the patient experienced the SAE of severe worsening septic shock. Study drug dose was not changed.

Discussions were held with the family, and the family signed a DNR on Day 7, and palliative extubation occurred on Day 8. The last dose of cefiderocol was administered at 12:34 hours on Day 8. EOT assessment was performed, and the outcome was considered a clinical failure with microbiological persistence.

The patient expired at 23:50 hours on Day 8. The death was considered as not related to study drug or procedure; the outcomes of the SAEs of worsening liver failure and worsening septic shock were reported as fatal.

AE = adverse event; APACHE = Acute Physiology and Chronic Health Evaluation;  
CPCR = cardiopulmonary cerebral resuscitation; CR = carbapenem resistance; DNR= Do not resuscitate; EA = Early Assessment; EOS = End of Study; EOT = End of Treatment; HBV = hepatitis B virus; IV = intravenous; MIC = minimum inhibitory concentration; NA = not available; PEA = pulseless electrical activity; q8h = every 8 hours; TOC = Test of Cure; VAP = ventilator-associated pneumonia

**Study qualifying diagnosis:** Ventilator-associated pneumonia due to *P. aeruginosa*, *C. indologenes*, *A. nosocomialis*, and *S. maltophilia*, with evidence of carbapenem resistance, due to treatment failure of CR-GNB with positive Chromogenic Media result.

**Study qualifying infection history:** At Screening/Baseline, *P. aeruginosa* resistant to ciprofloxacin and imipenem was identified from the sputum. The isolates were susceptible to amikacin, cefepime, ceftazidime-avibactam, ceftolozane-tazobactam, and colistin (Table 3). *C. indologenes*, *A. nosocomialis* and *S. maltophilia* were also identified from the sputum. The isolates were not susceptible to any tested antibiotics.

In parallel with this identification, the patient received empiric treatment with ceftazidime (unknown start date through Day -12), metronidazole (Day -14 to Day -7), meropenem (Day -12 to Day -4), tigecycline (Day -7 to Day -4), and colistin (Day -1 to Day 1).

**Current hospitalization history:** The patient was hospitalized on Day -4 from a clinic as an emergent admission into the intensive care unit due to VAP. The onset date of the infection was Day -18.

**Clinical course:** On Day -1, a microbiological laboratory specimen was obtained from the sputum, and WBC polymorphs (2+, 10-24, moderate) and squamous epithelial cells (1+, < 10, few) were noted. Gram-negative rods (+) were identified. The pathogens *A. nosocomialis* (semi-quantitation, 2+), *C. albicans* (semi-quantitation, 2+), *C. indologenes* (semi-quantitation, +), and *P. aeruginosa* (semi-quantitation, +) were identified.

On Day 1 (Screening/Baseline), a microbiological laboratory specimen was obtained from blood. The pathogen *Candida parapsilosis* was identified. Another microbiological laboratory specimen was obtained from the sputum. The pathogen *S. maltophilia* (semi-quantitation, +) was identified. A chest radiograph showed residual consolidation in both the right and left lungs and a pleural effusion of left lung (Table 5). The patient was on a ventilator; arterial blood gases (ABGs) were PaO<sub>2</sub> 97 mm Hg and PaCO<sub>2</sub> 29 mm Hg, SaO<sub>2</sub> 98%, and FiO<sub>2</sub> was 40%. Signs and symptoms at the initial clinical assessment showed severe fatigue, malaise, rales, and rhonchi; moderate bronchial breath sounds, dyspnea (including retractions), suctioned respiratory secretions, and dullness on percussion; and mild vomiting. The Sequential Organ Failure Assessment (SOFA) was 14, and the total Clinical Pulmonary Infection Score (CPIS) was 4 (Table 2). Inflammatory indices including WBC count, C-reactive protein (CRP), and body temperature were  $7.66 \times 10^9/\text{L}$ , 4.22 mg/dL, and 36.6°C, respectively (Table 1). The platelet count was  $18 \times 10^9/\text{L}$ , PT-INR was 6.27, and total bilirubin (TBL) was 15.2 mg/dL.

The patient was randomized to the cefiderocol treatment group and received 2 g, q8h beginning on Day 1. The patient received 20 subsequent infusions of cefiderocol (2 g, q8h) on Day 2 through Day 8.

On Day 1, the patient experienced the SAE of worsening liver failure. The dose of study medication was not changed. The event was Fatal. The investigator considered the event severe and not related to study medication. On Day 4 (EA), a microbiological laboratory

specimen was obtained from the sputum, and WBC polymorphs (3+,  $\geq 25$ , many) and squamous epithelial cells (1+,  $< 10$ , few) were noted. Gram-negative rods (+) were identified. The pathogens *P. aeruginosa* (semi-quantitation, +), *A. nosocomialis* (semi-quantitation, +), *S. maltophilia* (semi-quantitation, +), and *Candida albicans* (semi-quantitation, +) were identified. Another microbiological laboratory sample was obtained from the blood and the culture result was negative. The chest radiograph showed residual consolidation in the left and right lungs the lower lung showed partial resolution, and pleural effusion left lung; the lung fields compared to Screening were considered improved. The patient was on a ventilator; pulse oximetry revealed SpO<sub>2</sub> 100% and FiO<sub>2</sub> 25%. Signs and symptoms revealed moderate bronchial breath sounds, fatigue, malaise, rhonchi, and suctioned respiratory secretions. The SOFA was 12 and the Total CPIS was 2. The inflammatory indices included WBC count, CRP, and body temperature of  $5.46 \times 10^9/\text{L}$ , 3.26 mg/dL, and 36.0°C. The platelet count was  $11 \times 10^9/\text{L}$ , PT-INR was 5.18, TBL was 17.1 mg/dL. The patient was considered a clinical cure.

On Day 5, the patient experienced the SAE of worsening septic shock. The dose of study medication was not changed. The outcome was fatal. The investigator considered the event severe and not related to study medication.

Discussions were held with the family, and the family signed a DNR on Day 7. The last dose of cefiderocol was administered at 12:34 hours on Day 8.

On Day 8 (EOT), a microbiological laboratory specimen was obtained from the sputum, and WBC polymorphs (3+,  $\geq 25$ , many) and squamous epithelial cells (1+,  $< 10$ , few) were noted. Gram-negative rods (+) were identified. The pathogens *P. aeruginosa* (semi-quantitation, 2+), *A. nosocomialis* (semi-quantitation, 2+), and *S. maltophilia* (semi-quantitation, 2+) were identified. The chest radiograph showed residual consolidation in the right and left lungs, and a newly developed pneumonic path on the right middle lobe; the lung fields compared to Screening were considered worsened. The patient was on a ventilator; ABGs indicated PaO<sub>2</sub> 123 mm Hg, PaCO<sub>2</sub> 34 mm Hg, SaO<sub>2</sub> 99%, and FiO<sub>2</sub> 40%. Signs and symptoms revealed moderate fatigue, malaise, and suctioned respiratory secretions. The SOFA was 14 and the CPIS was 3. The inflammatory indices included a WBC count, CRP, and body temperature of  $13.97 \times 10^9/\text{L}$ , 2.17 mg/dL, and 35.4°C, respectively. The platelet count was  $17 \times 10^9/\text{L}$ , PT-INR was 3.81, TBL was 13.2 mg/dL. The patient was considered a clinical failure with microbiological persistence.

Palliative extubation occurred on the same date.

The patient died on the same day. The death was considered as not related to study drug or procedure; the outcomes of the SAEs of worsening liver failure and worsening septic shock were reported as fatal.

**Table 1 Inflammatory Indices**

Visit	White Blood Cell Count (RR = 3.9 to 10.6)	C-reactive Protein (RR = 0 to 0.5)	Body Temperature
Screening/Baseline	$7.66 \times 10^9/\text{L}$	4.22 mg/dL	36.6°C
Early Assessment	$5.46 \times 10^9/\text{L}$	3.26 mg/dL	36.0°C
End of Treatment	$13.97 \times 10^9/\text{L}$	2.17 mg/dL	35.4°C

RR = reference range

**Table 2 Sequential Organ Failure Assessment and Total Clinical Pulmonary Infection Score Status**

Visit	SOFA Score	Total CPIS
Screening/Baseline	14	4
Early Assessment	12	2
End of Treatment	14	3

CPIS = Clinical Pulmonary Infection Score; SOFA = Sequential Organ Failure Assessment

**Table 3**                      **Antimicrobial Susceptibility Testing at Screening  
(European Committee on Antimicrobial Susceptibility  
Testing)**

Pathogen	Resistant	Intermediate	Susceptible	Not Applicable
<i>Pseudomonas aeruginosa</i>	Ciprofloxacin, imipenem	Aztreonam, meropenem	Amikacin, cefepime, ceftazidime-avibactam, ceftolozane-tazobactam, colistin	Cefiderocol, tigecycline
<i>Acinetobacter nosocomialis</i>	Amikacin, ciprofloxacin, colistin, imipenem, meropenem	NA	NA	Aztreonam, cefepime, ceftazidime- avibactam, ceftolozane- tazobactam, cefiderocol, tigecycline
<i>Stenotrophomonas maltophilia</i>	NA	NA	NA	Amikacin, aztreonam, cefepime, ceftazidime- avibactam, ceftolozane- tazobactam, ciprofloxacin, colistin, imipenem, meropenem, cefiderocol, tigecycline
<i>Chryseobacteri indologenes</i>	NA	NA	NA	Amikacin, aztreonam, cefepime, ceftazidime- avibactam, ceftolozane- tazobactam, cefiderocol, ciprofloxacin, colistin, imipenem, meropenem, tigecycline

NA = not applicable

**Table 4 Susceptibility Testing at Each Visit**

Visit	IHMA Organism ID	AMK	AZT	CFPM	CAZ/ AVI	CEF/ TAZ	CPFX	CST	IPM	MEPM	CFDC	TGC
		MIC µg/mL										
Screening/ Baseline	<i>Pseudomonas aeruginosa</i> Sample ID E158433	8	16	4	2	0.5	1	1	16	8	0.12	4
Early Assessment	<i>Pseudomonas aeruginosa</i> Sample ID E158431	8	16	4	2	0.5	2	1	16	8	0.25	4
End of Treatment	<i>Pseudomonas aeruginosa</i> Sample ID E158427	8	8	4	2	0.5	1	1	16	8	0.12	> 4
Screening/ Baseline	<i>Acinetobacter nosocomialis</i> Sample ID E158425	32	32	> 16	8	16	> 4	4	64	> 64	64	4
Early Assessment	<i>Acinetobacter nosocomialis</i> Sample ID E158430	32	32	> 16	32	32	> 4	1	> 64	> 64	64	4
End of Treatment	<i>Acinetobacter nosocomialis</i> Sample ID E158426	32	32	> 16	4	32	2	1	> 64	> 64	64	> 4
Screening/ Baseline*	<i>Stenotrophomonas maltophilia</i> Sample ID E158429	8	> 32	> 16	32	32	4	≤ 0.5	> 64	> 64	0.06	0.5

Visit	IHMA Organism ID	AMK	AZT	CFPM	CAZ/AVI	CEF/TAZ	CPFX	CST	IPM	MEPM	CFDC	TGC
		MIC µg/mL										
Early Assessment	<i>Stenotrophomonas maltophilia</i> Sample ID E158432	8	32	> 16	32	32	4	1	> 64	> 64	0.06	0.5
End of Treatment	<i>Stenotrophomonas maltophilia</i> Sample ID E362815	64	> 32	> 16	> 64	64	2	1	> 64	> 64	0.25	≤ 0.25
Screening/ Baseline	<i>Chryseobacteri indologenes</i> Sample D E158428	> 64	32	> 16	> 64	> 64	> 4	> 8	> 64	> 64	0.5	4

AMK = amikacin; AZT = aztreonam; CFDC = cefiderocol; CPFX = ciprofloxacin; CAZ/AVI = ceftazidime-avibactam; CST = colistin; CEF/TAZ = ceftolozane-tazobactam; CFPM = cefepime; ID = identification; IHMA = International Health Management Associates; IPM = imipenem; MEPM = meropenem; MIC = minimum inhibitory concentration; TGC = tigecycline

\*Noted as an unscheduled visit. Sample number matches Screening/Baseline sample number.

**Table 5 Chest Radiograph Results**

Visit	Lung Fields/ Airways	Heart/ Vessels	Other Structures	Comparison of Lung Fields to Screening
Screening/ Baseline	Residual consolidation in the left and right lung. Pleural effusion left	NA	NA	NA
Early Assessment	Residual consolidation in the left and right lung; right lower lung showed partial resolution. Pleural effusion left	NA	NA	Improved
End of Treatment	Residual consolidation in the left and right lung. Newly developed pneumonic path on right middle lobe.	NA	NA	Worsened

NA = not applicable

**Table 6 Liver Function Tests**

Visit	AST (RR = 0 to 34)	ALT (RR = 10 to 49)	ALP (RR = 45 to 129)	GGT (RR = 0 to 72.9)	Total Bilirubin (RR = 0.32 to 1.2)
Screening/Baseline	37 IU/L	12 IU/L	136 IU/L	62 IU/L	15.2 mg/dL
Early Assessment	51 IU/L	17 IU/L	113 IU/L	62 IU/L	17.1 mg/dL
End of Treatment	71 IU/L	26 IU/L	132 IU/L	84 IU/L	13.2 mg/dL

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase;  
GGT = gamma-glutamyl transferase; RR = reference range

**Table 7 Renal Function Tests**

Visit	Blood Urea Nitrogen (RR = 9 to 23)	Serum Creatinine (RR = 0.7 to 1.3)	Creatinine Clearance
Screening/Baseline	59 mg/dL	1.1 mg/dL	77.5 mL/min
Early Assessment	67 mg/dL	1.2 mg/dL	71.04 mL/min
End of Treatment	101 mg/dL	1.9 mg/dL	44.87 mL/min

RR = reference range

**Table 8 Coagulation Tests**

Visit	Platelet Count (RR = 150 to 400)	aPTT (RR = 23.9 to 34.9)	PT-INR (RR: 0.85 to 1.15)
Screening/Baseline	$18 \times 10^9/L$	82.8 sec	6.27
Early Assessment	$11 \times 10^9/L$	111.6 sec	5.18
End of Treatment	$17 \times 10^9/L$	101.9 sec	3.81

aPTT = activated partial thromboplastin time; PT-INR = prothrombin international normalized ratio;  
RR = reference range

## Subject ID Patient # 28

Patient ID		Patient # 28	Country		Taiwan	
Age		71	Clinical Diagnosis at Screening		VAP	
Gender		Female	Severity		Severe	
Race		Asian	APACHE II Score		23	
Height (cm)		147.0	Causative Pathogen at Screening		Acinetobacter nosocomialis	
Body Weight (kg)		46.0	CR Evidence at Screening (other than central lab)		Treatment failure CR-GNB (Rapidec Carba NP)	
MIC of Meropenem		> 64 µg/mL	MIC of Cefiderocol		0.5 µg/mL	
MIC of Imipenem		64 µg/mL				
Duration of Study Treatment		3 days	Standard of Care		Colistin (66.8 mg IV), tigecycline (50 mg IV)	
Study Drug Treatment		Cefiderocol (2g q8h IV)				
Microbiological Results at TOC			Day 28 All-cause Mortality		Clinical Outcome at TOC	
Indeterminate			Death (Day 3)		Clinical failure	
Medical History (Ongoing)	Hypertension ; lung cancer, adenocarcinoma, LUL ; left renal cyst ; pressure sore at coccyx, upper lip, adult respiratory distress syndrome ; hypokalemia, tachycardia ; limbs pitting edema ; skin rash at chest area ; acute respiratory failure ; bilateral pleural effusion, new onset diagnosis with pneumonia at RUL ; diarrhea					
Medical History (Not Ongoing)	Fallopian tube ligation ; lobectomy ; radical lobectomy, extended lymph node dissection; pneumonia RUL and LLL type of HCAP, acute respiratory failure, septic shock ; tracheostomy ; bronchoscope: right endobronchial tree, an endobronchial lesion over RB3					
Adverse Event	Day	Severity	Action Taken with Study Drug	Outcome	Causality	Serious
Acute kidney injury	2	Mild	Dose not changed	Not recovered/not resolved	Not related	No
Multiple organ failure	2	Severe	Dose not changed	Fatal	Not related	Yes
Aggravation of VAP	2	Severe	Dose not changed	Fatal	Not related	Yes
Narrative Summary						
<p>A 71-year-old Asian female from Taiwan had lung adenocarcinoma (LUL) (rT2N2M1, Stage IV) and underwent a radial lobectomy with extended lymph node dissection on Day -53.</p> <p>The patient was admitted to the study site ICU on Day -20 and mechanically ventilated on the day of admission with the diagnosis of HCAP, adult respiratory distress syndrome, acute respiratory failure, and septic shock. A pressure sore of the coccyx and upper lip was reported on Day -20, size and staging was not provided. The HCAP was successfully treated with piperacillin/tazobactam and isepamicin, and she was extubated on Day -10.</p> <p>A skin rash of the chest was reported on Day -10. However, she developed shortness of breath on Day -8, and was intubated again and underwent a tracheostomy on Day -6. On Day -2, a bronchoscopy of the right endobronchial tree was performed and results showed an endobronchial lesion over RB3; patient experienced bilateral pleural effusion. On Day -2, the patient was diagnosed with VAP due to carbapenem-resistant <i>Acinetobacter baumannii</i>. The patient was randomized to the cefiderocol group on</p>						

Day 1. Treatment with cefiderocol (2 g, q8h) was initiated. The patient received 4 subsequent infusions of cefiderocol on Days 1 to 3, respectively. Chest x-ray taken on Day 1 showed diffuse increased infiltration. Her condition was deteriorating progressively, mainly as hypoxemia and respiratory failure, and she was considered a clinical failure.

The patient was reported to have unrelated severe SAEs of aggravation of VAP and multiple organ failure on Day 2. The patient developed the unrelated mild AE of acute kidney injury and experienced oliguria on Day 2.

On Day 3, the patient died due to aggravation of VAP and multiple organ failure. The death was considered not related to study drug or procedures.

AE = adverse event; APACHE=Acute Physiology and Chronic Health Evaluation; ARDS = acute respiratory distress syndrome; CR = carbapenem resistance; GNB = Gram-negative bacteria; HCAP = healthcare-associated pneumonia; ICU = intensive care unit; ID = identification; IV = intravenous; LLL = left lower lung; LUL = left upper lung; MIC = minimum inhibitory concentration; q8h = every 8 hours; RUL = right upper lung; SAE = serious adverse event; TOC = Test of Cure; VAP = ventilator-associated pneumonia

**Study qualifying diagnosis:** Ventilator-associated pneumonia due to *A. nosocomialis* with evidence of carbapenem resistance through treatment failure of CR-GNB.

**Study qualifying infection history:** Three days prior to Screening, a tracheal aspirate showed *A. nosocomialis* that was resistant to ciprofloxacin, imipenem, meropenem, and amikacin (Table 3). The isolate was susceptible to colistin.

**Current hospitalization history:** The patient was hospitalized on Day -20 to the ICU due to the current infection. The patient was diagnosed with septic shock. The patient was treated successfully with empiric piperacillin/tazobactam up to Day -13 and isepamicin from Day -19 to Day -12). The patient was extubated on Day -10, but had to be re-intubated on Day -8. The onset date of the VAP was Day -2.

On Day -6, the patient had a tracheostomy.

On Day -2, the patient was diagnosed with VAP with presentation of infiltration over the right upper lobe and left side diffuse infiltration in the chest radiograph. The patient was empirically treated with imipenem/cilastatin 500 mg from Day -2 to Day -1 and piperacillin/tazobactam on Day -2 only. On Day -1, a diagnosis of VAP due to carbapenem-resistant *A. baumannii* was made.

**Clinical course:** On Days -3 and -1, respectively, a microbiological laboratory specimen was obtained from the tracheal aspirate and white blood cell (WBC) polymorphs (3+,  $\geq 25$ , many) and squamous epithelial cells (1+,  $< 10$ , few) were noted. Gram-negative rods (+) were identified in the Day -3 sample. The pathogen *A. nosocomialis* was identified on both days (no quantitation, light growth on Day -1).

On Day 1, the chest radiograph showed diffuse increased infiltration (Table 5). The patient was on a ventilator. Arterial blood gases (ABGs) obtained showed PaO<sub>2</sub> 73 mm Hg, PaCO<sub>2</sub> 51 mm Hg, SaO<sub>2</sub> 96% and FiO<sub>2</sub> 60%. Signs and symptoms at the initial clinical assessment included moderate fatigue, malaise, expectorated sputum production, suctioned respiratory secretions, and rhonchi; severe dyspnea (including retractions); and mild cough and chest skin rash. The Sequential Organ Failure Assessment (SOFA) score was 3 and the Clinical

Pulmonary Infection Score Status (CPIS) was 7 (Table 2). The inflammatory indices of WBC count, C-reactive protein (CRP), and body temperature were  $21.69 \times 10^9/L$ , 12.73 mg/dL, and 36.8°C, respectively (Table 1).

Treatment with cefiderocol (2 g, q8h) was initiated. The patient received 4 subsequent infusions of cefiderocol on Days 1 to 3.

On Day 2, aggravation of VAP and multiple organ failure were reported as SAEs. The patient developed acute kidney injury and oliguria.

Her condition was deteriorating progressively, mainly as hypoxemia and respiratory failure, and she was considered a clinical failure. On Day 3, the patient died due to aggravation of VAP and multiple organ failure. The investigator considered the events not related to study drug.

**Table 1 Inflammatory Indices**

Visit	White Blood Cell Count (RR = 4 to 11)	C-reactive Protein (RR = 0 to 0.3)	Body Temperature
Screening/Baseline	$21.69 \times 10^9/L$	12.73 mg/dL	36.8°C
Early Assessment	NA	NA	36.5°C

NA = not available; RR = reference range

**Table 2 Sequential Organ Failure Assessment and Total Clinical Pulmonary Infection Score Status**

Visit	SOFA Score	Total CPIS
Screening/Baseline	3	7

CPIS = Clinical Pulmonary Infection Score; SOFA = Sequential Organ Failure Assessment

**Table 3 Antimicrobial Susceptibility Testing at Screening (European Committee on Antimicrobial Susceptibility Testing)**

Pathogen	Resistant	Intermediate	Susceptible	Not Applicable
<i>Acinetobacter nosocomialis</i>	Amikacin, ciprofloxacin, imipenem, and meropenem	None	Colistin	Aztreonam, ceftazidime-avibactam, ceftolozane-tazobactam, cefiderocol, cefepime, and tigecycline

**Table 4 Susceptibility Testing at Each Visit**

Visit	IHMA Organism ID	AMK	AZT	CFPM	CAZ/ AVI	CEF/ TAZ	CPFX	CST	IPM	MEPM	CFDC	TGC
		MIC µg/mL										
Screening/ Baseline	<i>A. nosocomialis</i> Sample ID E295914	32	16	16	8	8	> 4	1	64	> 64	0.5	4

AMK = amikacin; AZT = aztreonam; CAZ/AVI = ceftazidime-avibactam; CEF/TAZ = ceftolozane-tazobactam; CFDC = cefiderocol; CFPM = cefepime; CPFX = ciprofloxacin; CST = colistin; ID = identification; IHMA = International Health Management Associates; IPM = imipenem; MEPM = meropenem; MIC = minimum inhibitory concentration; TGC = tigecycline

**Table 5 Chest Radiograph Results**

Visit	Lung Fields/ Airways	Heart/ Vessels	Other Structures	Comparison of Lung Fields to Screening
Screening/ Baseline	Diffuse increased infiltration	NA	NA	NA

NA = not applicable

**Table 6 Liver Function Tests**

Visit	AST (RR = 8 to 38)	ALT (RR = 10 to 35)	ALP (RR = 50 to 190)	GGT (RR = 4 to 63)	Total Bilirubin (RR = 0.2 to 1.2)
Screening/Baseline	47 U/L	63 U/L	324 U/L	132 U/L	0.5 mg/dL

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase;  
GGT = gamma-glutamyl transferase; RR = reference range

**Table 7 Renal Function Tests**

Visit	Blood Urea Nitrogen (RR = 5 to 25)	Serum Creatinine RR = 0.5 to 0.9)	Creatinine Clearance
Screening/Baseline	32 mg/dL	0.71 mg/dL	52.78 mL/min

RR = reference range

**Table 8 Coagulation Tests**

Visit	Platelet Count (RR = 150 to 400)	aPTT (RR = 24.3 to 32.7)	PT-INR (RR = 0.85 to 1.15)
Screening/Baseline	$397 \times 10^9/L$	23.4 sec	1.09

aPTT = activated partial thromboplastin time; PT-INR = prothrombin international normalized ratio;  
RR = reference range

## Subject ID Patient # 29

Subject ID	Patient # 29	Country	Taiwan			
Age	54	Clinical Diagnosis at Screening	VAP			
Gender	Male	Severity	Severe			
Race	Asian	APACHE II Score	13			
Height (cm)	168	Causative Pathogen at Screening	Acinetobacter baumannii			
Body Weight (kg)	55	CR Evidence at Screening (other than central lab)	Treatment failure CR-GNB (chromogenic media)			
MIC of Meropenem	64 µg/mL	MIC of Cefiderocol	16 µg/mL			
MIC of Imipenem	64 µg/mL					
Duration of Study Treatment	14 days	Standard of Care	Colistin (133.6 mg IV)			
Study Drug Treatment	Cefiderocol (2 g q8h IV)					
Microbiological Results at TOC		Day 28 All-cause Mortality	Clinical Outcome at TOC			
Persistence (EOT)		Expired (Day 18)	Clinical failure (EOT)			
Medical History (Ongoing)	Hypertension, alcoholism, hepatitis B, lung cancer, carcinoma, poorly differentiated (NOS), left upper limb, cT3N3M0, Stage IIIB, left upper limb deep vein thrombosis, s/p enoxaparin, brain metastasis progressed, rT3N0M1b, Stage IV, hypotension, suspected COPD, hypomagnesemia, pressure sores on sacral bone, bilateral ankles, occipital bone and bilateral ears, hypovolemia, septic shock, penis skin wound, prothrombin time prolonged suspect infection related or enoxaparin related, leg edema, pressure sore right cheek, right leg bruising, diarrhea, constipation, pressure sore right wrist skin, irritable mood, poor oxygenation respiratory failure					
Medical History (Not Ongoing)	Left total hip replacement, avascular necrosis s/p total hip replacement, bilateral lung bulla, s/p VATS with right lung volume reduction and left bullectomy and intra-pulmonary adhesions lysis, subcutaneous emphysema over left chest wall and neck s/p VATS intrapulmonary adhesions lysis s/p chest tube, pneumothorax, left side s/p thoracoscopic pleurectomy, pneumolysis, hyponatremia, bilateral pneumonia, respiratory failure, respiratory acidosis, hypokalemia, atrial fibrillation					
Adverse Event	Day	Severity	Action Taken with Study Drug	Outcome	Causality	Serious
Upper GI bleeding	4	Mild	Dose not changed	Recovering/resolving	Related	No
Baseline ALT 54, elevated to 145	4	Mild	Dose not changed	Recovering/resolving	Related	No
AST 44 from Baseline, elevated to 106	10	Mild	Dose not changed	Recovering/resolving	Related	No
Right pneumothorax	14	Moderate	Dose not changed	Recovering/resolving	Not related	No
Bacteremia	14	Severe	Dose not changed	Fatal	Not related	Yes

VAP - left lung	14	Severe	NA	Fatal	Not related	Yes
Hyperglycemia	16	Mild	NA	Recovering/ resolving	Not related	No

#### Narrative Summary

A 54-year-old male had a medical history of a left hip total hip replacement, avascular necrosis s/p total hip replacement, and bilateral lung bulla, right lung volume reduction surgery and left bullectomy with VATS. The patient was diagnosed with Stage IIIB lung cancer (poorly differentiated carcinoma, not otherwise specified); alcoholism, and hepatitis B. The patient developed a left upper limb deep vein thrombosis s/p enoxaparin on and had a pneumothorax (left side) s/p thoroscopic pleurectomy and pneumolysis. Approximately 8 months later, he developed brain metastasis (rT3N0M1b, Stage IV).

The patient was hospitalized on Day -11 due to progressive shortness of breath for 1 month (exacerbation within the past 2 weeks). The chest x-ray showed a bilateral increase in infiltration, and the patient was diagnosed to have bilateral pneumonia, septic shock, hypomagnesemia, hyponatremia, and respiratory failure on Day -10. Suspected COPD was reported. He was intubated on Day -10. Piperacillin/tazobactam and levofloxacin were administered on Day -10, and levofloxacin was stopped on Day -7. Several pressure sores (occipital, sacral, bilateral ankles, bilateral ears [staging not specified]) were reported on the same date, Day -10. Bilateral leg edema 2+ was reported on the next day with prothrombin time prolong suspect infection related or enoxaparin related. A pressure sore of the right cheek and right leg bruising was reported on Day -7. A pressure sore of the right wrist skin was reported on Day -5. Once the bilateral pneumonia improved and the patient was extubated on Day -4 and placed on BiPAP/nasal high-flow oxygen. Piperacillin/tazobactam was administered until Day 1; however, the antibiotic treatment failed, and on Day -1, the patient was re-intubated due to dyspnea with sinus tachycardia (poor oxygenation respiratory failure was reported on Day -1. Chest x-ray showed new onset pneumonia over right lung Day -1). TA culture collected on Day -2 isolated *A. baumannii*. CR was confirmed by treatment failure CR-GNB (chromogenic media).

He was enrolled in this study and randomized to the cefiderocol arm on Day 1. The patient received cefiderocol 2 g q8h IV from Day 1 and completed treatment with cefiderocol on Day 14.

On Day 4 (EA), TA culture showed the pathogen *A. baumannii* (no quantitation, heavy growth). It was also reported that the patient vomited blood clot-like gastric contents and the mild AE of upper GI bleeding was reported. On the same date, ALT elevation was observed, and the AE of Baseline ALT: 54 elevated to 145 was reported, which was considered related to the study drug by the investigator. Dose was not changed. The VAP did not improve. On Day 10, he had AST elevation and the mild AE of AST: 44 from Baseline, elevated to 106 was reported, which was also considered related to the study drug. Dose was not changed.

On Day 14, he developed a right pneumothorax. Blood cultures showed carbapenem-resistant *A. baumannii*. The unrelated severe SAE of bacteremia was reported on Day 14; study drug dose was not changed.

On Day 15 (EOT), clinical outcome showed clinical failure; microbiologic outcome showed persistence. On the same date, the unrelated severe SAE of VAP of the left lung was reported. Colistin was started for the treatment of the bacteremia. On Day 16, a chest x-ray revealed diffuse infiltrates and a right side pigtail chest tube.

On Day 18, the patient expired with bacteremia, pneumonia, and poor oxygenation, 4 days after receiving his last dose of cefiderocol.

AE = adverse event; ALT = alanine aminotransferase; APACHE = Acute Physiology and Chronic Health Evaluation; AST = aspartate aminotransferase; BiPAP = bi-level positive airway pressure; COPD = chronic obstructive pulmonary disease; CR = carbapenem resistance; EA= Early Assessment; EOT= End of Treatment; GI = gastrointestinal; GNB = Gram-negative bacteria; HAP = hospital-acquired pneumonia; ID = identification; IV = intravenous; MIC = minimum inhibitory concentration; NOS = not otherwise specified; q8h = every 8 hours; SAE = serious adverse event; s/p = status post; TA = tracheal aspirate; TOC = Test of Cure; VAP = ventilator-associated pneumonia; VATS = video-assisted thoracoscopic surgery

**Study qualifying diagnosis:** Ventilator-associated pneumonia due to *A. baumannii* was identified with evidence of CR using chromogenic media after treatment failure of CR-GNB.

**Study qualifying infection history:** At the Screening/Baseline visit, a TA sample showed *A. baumannii* resistant to amikacin, ciprofloxacin, imipenem, and meropenem. The isolate was susceptible to colistin (Table 3).

**Current hospitalization history:** The patient was hospitalized on Day -11 from home on an emergent basis for the current infection and admitted to the intensive care unit (ICU) the next day. Ventilation was initiated on Day -10 and continued through his death on Day 18. The onset date of the infection was Day 1 .

**Clinical course:** On Day 1, Screening/Baseline), a microbiological laboratory specimen was obtained from the TA, and white blood cell (WBC) polymorphs (3+,  $\geq 25$ , many) and squamous epithelial cells (2+, 10 to 24, moderate) were noted. Gram-negative rods (3+) were identified. The pathogen *A. baumannii* (no quantitation, heavy growth) was identified. The chest radiograph showed increased infiltration over the right middle lung field and left lung field on Day 1. Also noted was alveolar infiltrate over the right middle lung field (Table 5). The patient was under mechanical ventilation; arterial blood gases (ABGs) showed PaO<sub>2</sub> 92 mm Hg, PaCO<sub>2</sub> 35 mm Hg, SaO<sub>2</sub> 98%, and FiO<sub>2</sub> 35%. Signs and symptoms at the initial clinical assessment showed mild cough and rhonchi, and moderate dyspnea (including retractions), expectorated sputum production, and suctioned respiratory secretions. The Sequential Organ Failure Assessment (SOFA) score was 7, and the Clinical Pulmonary Infection Score (CPIS) was 5 (Table 2). The inflammatory indices of WBC count, C-reactive protein (CRP), and body temperature were  $11.05 \times 10^9/L$ , 20.390 mg/dL, and 37.6°C, respectively (Table 1).

Treatment with cefiderocol 2g q8h IV was initiated on Day 1. The patient received 38 subsequent infusions of cefiderocol from Days 2 through 14 .

On Day 4 ( EA) a microbiological laboratory specimen was obtained from the TA, and WBC polymorphs (3+,  $\geq 25$ , many) and squamous epithelial cells (2+, 10 to 24, moderate) were noted. Gram-negative rods (+) were identified. The pathogen *A. baumannii* (no quantitation, heavy growth) was identified. The chest radiograph did not change compared with the Screening/Baseline visit and still showed infiltration on the right side. The patient was kept on mechanical ventilation; ABGs showed PaO<sub>2</sub> 83 mm Hg, PaCO<sub>2</sub> 35 mm Hg, SaO<sub>2</sub> 97%, and FiO<sub>2</sub> 35%. Signs and symptoms included mild cough, expectorated sputum production, rhonchi, and moderate suctioned respiratory secretions. The SOFA score and CPIS were decreased to 5 and 4, respectively. The inflammatory indices of WBC count, CRP, and body temperature were  $9.54 \times 10^9/L$ , 21.250 mg/dL, and 38.4°C, respectively. The clinical outcome was clinical failure. On Day 4, the patient had upper GI bleeding and ALT elevation, which were considered related to the study drug by the investigator.

On Day 10, (Unscheduled Visit), the patient experienced the AE of AST elevation, which was also considered related to the study drug. The baseline ALT level was 54 U/L and increased to 145 U/L. The chest radiograph showed diffuse bilateral infiltrates, and the

lung fields were considered worsened compared to Screening. The ABGs showed PaO<sub>2</sub> 83 mm Hg, PaCO<sub>2</sub> 65 mm Hg, SaO<sub>2</sub> 95%, and FiO<sub>2</sub> 60%.

On Day 13 (Unscheduled Visit), the chest radiograph showed diffuse bilateral infiltrates, and the lung fields were considered worsened compared to Screening. The ABGs showed PaO<sub>2</sub> 67 mm Hg, PaCO<sub>2</sub> 50 mm Hg, SaO<sub>2</sub> 94%, and FiO<sub>2</sub> 45%.

On Day 14 (Unscheduled Visit), a microbiological laboratory specimen was obtained from the blood. Gram-negative rods (+) were identified. The pathogen *A. baumannii* was identified. The chest radiograph showed a right pneumothorax with diffuse bilateral infiltrates. The patient experienced a right pneumothorax and the SAE of bacteremia. The investigator considered the pneumothorax moderate and the bacteremia severe. The dose of study drug was not changed due to either event. The patient was recovering from the pneumothorax. The ABGs indicated PaO<sub>2</sub> 50 mm Hg, PaCO<sub>2</sub> 34 mm Hg, SaO<sub>2</sub> 91%, and FiO<sub>2</sub> 100%.

On Day 15 (EOT), a microbiological laboratory specimen was obtained from the TA, and WBC polymorphs (3+,  $\geq 25$ , many) and squamous epithelial cells (2+, 10 to 24, moderate) were noted. Gram-negative rods (5+) were identified. The pathogen *A. baumannii* (no quantitation, heavy growth) was identified. The chest radiograph an increase of infiltrates over the left side, a pigtail chest tube on the right side, and the lung fields compared to Screening had worsened. The patient was on mechanical ventilation. The patient's oxygenation deteriorated; ABGs showed PaO<sub>2</sub> 65 mm Hg, PaCO<sub>2</sub> 46 mm Hg, SaO<sub>2</sub> 95%, and FiO<sub>2</sub> 60%. Signs and symptoms included moderate dyspnea (including retractions) and suctioned respiratory secretions. The SOFA score was 7, and the CPIS was 5. The inflammatory indices of WBC count, CRP, and body temperature did not improve;  $11.88 \times 10^9/L$ , 30.6 mg/dL, and 36.5°C, respectively. The clinical outcome was clinical failure. The microbiologic outcome was persistence. On the same day, the patient developed the serious event of VAP (left lung). The event was considered by the investigator to be not related to the study drug colistin was started.

On Day 16, a chest radiograph revealed diffuse infiltrates and right side pigtail chest tube, and the lung fields were considered worsened compared to Screening.

On Day 17, a microbiological laboratory specimen was obtained from the anus, and the culture result was negative. The ABGs showed PaO<sub>2</sub> 47 mm Hg, PaCO<sub>2</sub> 57 mm Hg, SaO<sub>2</sub> 82%, and FiO<sub>2</sub> 60%.

On Day 18 (End of Study), the patient expired with bacteremia, pneumonia, and poor oxygenation, 4 days after receiving his last dose of cefiderocol.

**Table 1 Inflammatory Indices**

Visit	White Blood Cell Count (RR = 4 to 11)	C-reactive Protein (RR = 0 to 0.3)	Body Temperature
Screening/Baseline	$11.05 \times 10^9/\text{L}$	20.390 mg/dL	37.6°C
Early Assessment	$9.54 \times 10^9/\text{L}$	21.250 mg/dL	38.4°C
End of Treatment	$11.88 \times 10^9/\text{L}$	30.600 mg/dL	36.5°C

RR = reference range

**Table 2 Sequential Organ Failure Assessment and Total Clinical Pulmonary Infection Score Status**

Visit	SOFA Score	CPIS
Screening/Baseline	7	5
Early Assessment	5	4
End of Treatment	7	5

CPIS = Clinical Pulmonary Infection Score; SOFA = Sequential Organ Failure Assessment

**Table 3 Antimicrobial Susceptibility Testing at Screening (European Committee on Antimicrobial Susceptibility Testing)**

Pathogen	Resistant	Intermediate	Susceptible	Not Applicable
<i>Acinetobacter baumannii</i>	Amikacin, ciprofloxacin, imipenem, meropenem	NA	Colistin	Aztreonam, ceftazidime- avibactam, ceftolozane- tazobactam, cefiderocol, tigecycline, cefepime

NA = not applicable

**Table 4 Susceptibility Testing at Each Visit**

Visit	IHMA Organism ID	AMK	AZT	CFPM	CAZ/AVI	CEF/TAZ	CPFX	CST	IPM	MEPM	CFDC	TGC
		MIC µg/mL										
Screening/ Baseline	<i>Acinetobacter baumannii</i> Sample ID E478080	> 64	32	> 16	32	32	> 4	≤ 0.5	64	64	16	1
Early Assessment	<i>Acinetobacter baumannii</i> Sample ID E478079	> 64	32	> 16	32	16	> 4	≤ 0.5	64	64	16	1
End of Treatment	<i>Acinetobacter baumannii</i> Sample ID E478078	> 64	> 32	> 16	> 64	32	> 4	1	64	64	8	1

AMK = amikacin; AZT = aztreonam; CAZ/AVI = ceftazidime-avibactam; CEF/TAZ = ceftolozane-tazobactam; CFDC = cefiderocol; CFPM = cefepime; CPFX = ciprofloxacin; CST = colistin; ID = identification; IHMA = International Health Management Associates; IPM = imipenem; MEPM = meropenem; MIC = minimum inhibitory concentration; TGC = tigecycline

**Table 5 Chest Radiograph Results**

Visit	Lung Fields/ Airways	Heart/ Vessels	Other Structures	Comparison of Lung Fields to Screening
Screening/ Baseline	Increased infiltration over right middle lung field and left lung field on Day 1. Alveolar infiltrate over right middle lung field	NA	NA	NA
Early Assessment	Still some infiltration on right side	NA	Still some infiltration on right side	No change
Day 10	Diffuse bilateral infiltrates	NA	NA	Worsened
Day 13	Diffuse bilateral infiltrates	NA	NA	Worsened
Day 14	Right pneumothorax, diffuse bilateral infiltrates	NA	NA	Worsened
End of Treatment	Increased infiltration over left side; pigtail chest tube right side	NA	NA	Worsened
Day 16	Diffuse infiltrates, right side pigtail chest tube	NA	NA	Worsened

NA = not applicable

**Table 6 Liver Function Tests**

Visit	AST (RR = 8 to 38)	ALT (RR = 10 to 50)	ALP (RR = 50 to 190)	GGT (RR = 4 to 63)	Total Bilirubin (RR = 0.2 to 1.2)
Screening/Baseline	44 U/L	54 U/L	99 U/L	240 U/L	0.5 mg/dL
Early Assessment	88 U/L	145 U/L	149 U/L	259 U/L	0.3 mg/dL
Day 10	106 U/L	226 U/L	193 U/L	NA	NA
Day 14	NA	88 U/L	NA	NA	0.2 mg/dL
End of Treatment	21 U/L	58 U/L	105 U/L	127 U/L	0.3 mg/dL

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyl transferase; NA = not available; RR = reference range

**Table 7 Renal Function Tests**

Visit	Blood Urea Nitrogen (RR = 5 to 25)	Serum Creatinine (RR = 0.7 to 1.4)	Creatinine Clearance
Screening/Baseline	27 mg/dL	1.05 mg/dL	62.57 mL/min
Early Assessment	27 mg/dL	0.76 mg/dL	86.44 mL/min
Day 10	31 mg/dL	0.75 mg/dL	NA
Day 14	26 mg/dL	0.59 mg/dL	NA
End of Treatment	26 mg/dL	0.57 mg/dL	115.25 mL/min

NA = not available; RR = reference range

**Table 8**                      **Coagulation Tests**

<b>Visit</b>	<b>Platelet Count (RR = 150 to 400)</b>	<b>aPTT (RR = 24.3 to 32.7)</b>	<b>PT-INR (RR = 0.85 to 1.15)</b>
Screening/Baseline	$135 \times 10^9/\text{L}$	30.4 sec	1.31
Early Assessment	$183 \times 10^9/\text{L}$	25.1 sec	1.22
Day 10	$120 \times 10^9/\text{L}$	NA	NA
Day 14	$121 \times 10^9/\text{L}$	NA	NA
End of Treatment	$117 \times 10^9/\text{L}$	26.9 sec	1.24

aPTT = activated partial thromboplastin time; NA = not available; PT-INR = prothrombin international normalized ratio; RR = reference range

## Subject ID Patient # 30

Patient ID		Patient # 30	Country		Republic of Korea	
Age		71	Clinical Diagnosis at Screening		HAP	
Gender		Male	Severity		Moderate	
Race		Asian	APACHE II Score		20	
Height (cm)		160.0	Causative Pathogen at Screening		Acinetobacter baumannii	
Body Weight (kg)		50.0	CR Evidence at Screening (other than central lab)		Treatment failure CR-GNB	
MIC of Meropenem		> 64 µg/mL	MIC of Cefiderocol		0.25 µg/mL	
MIC of Imipenem		> 64 µg/mL				
Duration of Study Treatment		3 days	Standard of Care		Colistin (150 mg IV)	
Study Drug Treatment		Cefiderocol (2 g IV q8h)				
Microbiological Results at TOC			Day 28 All-cause Mortality		Clinical Outcome at TOC	
Indeterminate			Death (Day 3)		Clinical failure (EA)	
Medical History (Ongoing)	Gastroesophageal reflux disease; hypertension; Parkinsonism; external hemorrhoid; diabetes mellitus; status epilepticus; adrenal insufficiency; general weakness; hypokalemia; ileus; hypomagnesemia; acidosis, pulmonary edema; hypoalbuminemia, hypocalcemia; pseudomembranous colitis; septic shock					
Medical History (Not Ongoing)	Stomach cancer; L-spine compression; pseudomembranous colitis; diarrhea; hiccup; septic shock					
Adverse Event	Day	Severity	Action Taken with Study Drug	Outcome	Causality	Serious
Aggravated pneumonia	1	Severe	Dose not changed	Fatal	Not related	Yes
Narrative Summary						
<p>A 71-year-old Asian male from Korea had a medical history of gastroesophageal reflux disease, stomach cancer, L-spine compression, Parkinsonism, diabetes mellitus, status epilepticus, and adrenal insufficiency.</p> <p>The patient was admitted from a nursing facility on Day -91 due to general weakness and was discharged and then transferred on Day -77 back to the skilled nursing facility.</p> <p>On Day -47, the patient was admitted and then transferred on Day -46 to the ICU of the study site for close monitoring. The patient developed diarrhea on Day -47, was diagnosed as having with pseudomembranous colitis on Day -45, and later developed ileus on Day -43. The patient was in septic shock and developed pulmonary edema on Day -13. Meropenem was administered from Day -13 to Day 1. The causative pathogen for sepsis was not identified. Metronidazole IV and oral vancomycin were used to treat colitis concurrently with pneumonia treatment.</p> <p>The patient developed HAP on Day-6.</p> <p>The culture results were available on Day 1 demonstrating carbapenem-resistant <i>A. baumannii</i>. The patient was considered treatment failure and enrolled in the study. The patient was randomized to the cefiderocol group. The patient developed septic shock on Day 1, the day of randomization. He received a total of 3 days of cefiderocol without Gram-negative adjunctive antibiotics. Metronidazole and vancomycin were continued until Day 2 and Day 3, respectively, for pseudomembranous colitis.</p> <p>On Day 1, the SAE of aggravated pneumonia was reported. Dose was not changed.</p> <p>On Day 3 (EA), a microbiological laboratory specimen was obtained from the sputum, and the culture</p>						

result was negative. The patient was considered a clinical failure.

On the same day, Day 3, the patient's condition deteriorated due to the progression of the pneumonia, and hypotension developed despite use of inotropics. The patient died on Day 3, while receiving the sixth dose of the study drug. The cause of death was considered as aggravated pneumonia by the investigator.

APACHE=Acute Physiology and Chronic Health Evaluation; CR = carbapenem resistance; EA = Early Assessment; GNB = Gram-negative bacteria; HAP = hospital-acquired pneumonia; ICU = intensive care unit; ID = identification; IV = intravenous; MIC = minimum inhibitory concentration; q8h = every 8 hours; SAE = serious adverse event; TOC = Test of Cure; unk = unknown

**Study qualifying diagnosis:** Hospital-acquired pneumonia due to *A. baumannii* identified to be carbapenem resistant through treatment failure of CR-GNB.

In parallel with this identification, the patient was treated with meropenem from Days -13 to -1.

**Study qualifying infection history:** A sputum sample collected at the Screening/Baseline visit indicated *A. baumannii* resistant to amikacin, ciprofloxacin, colistin, imipenem, and meropenem (Table 3).

**Current hospitalization history:** The patient was admitted from a nursing facility on Day -91 due to general weakness. On Day -46, the patient was admitted to ICU of the study site for close monitoring. The patient developed diarrhea on Day -47 and was diagnosed as having pseudomembranous colitis on Day -45. He also developed ileus on Day -43. The onset date of the HAP infection was Day -6.

The patient developed septic shock and pulmonary edema on Day -13. The patient was treated with meropenem IV 1 g every 12 hours (q12h) from Day -13 to Day -11; and vancomycin IV 1 g q12h on Day -13, 1 g once on Day -12 and 1 g q12h on Day -11. For the septic shock he was treated with norepinephrine 40 mg every 24 hours (q24h) from Day -13 to Day -7, and for the pulmonary edema he received furosemide 140 mg on an as-needed basis beginning on Day -13.

On Day -8, the patient started receiving treatment for pseudomembranous colitis. He received metronidazole IV 500 mg q12h on Day -8, 500 mg q8h on Day -7 to Day -1, 500 mg q12h on Day 1, and 500 mg q24h on Day 1 to Day 2. He also received vancomycin 500 mg orally q12h on Day -8, 500 mg every 6 hours from Day -7 to Day 2, and 500 mg once on Day 3 for pseudomembranous colitis.

**Clinical course:** On Day 1 (Screening/Baseline), a microbiological laboratory specimen was obtained from the sputum, and white blood cell (WBC) polymorphs (3+,  $\geq 25$ , many) and squamous epithelial cells (1+,  $< 10$ , few) were noted. Gram-negative rods (+) were identified. The pathogen *A. baumannii* (no quantitation, heavy growth) was identified. The chest radiograph showed consolidation in both lung fields (Table 5). Pulse oximetry revealed SpO<sub>2</sub> 100%, and FiO<sub>2</sub> 28%. Signs and symptoms at the initial clinical assessment included severe suctioned respiratory secretions and moderate dyspnea (including retractions), expectorated sputum production, and rales. The Sequential Organ Failure Assessment (SOFA) score was 8 and the Clinical Pulmonary Infection Score Status

(CPIS) was 5 (Table 2). The inflammatory indices of WBC count, C-reactive protein (CRP), and body temperature were  $19.63 \times 10^9/L$ , 17.16 mg/dL, and 38.1°C, respectively (Table 1).

The patient experienced another episode of septic shock on Day 1, and it was treated with norepinephrine 40 mg q24h IV from Day 1 to Day 2, norepinephrine 17.5 mg once IV, vasopressin 4.2 U once IV, epinephrine 4.5 mg as needed IV, and atropine 0.5 mg once IV, all on Day 3. The patient was also reported to have a SAE of aggravated pneumonia on Day 1.

The patient was randomized to the cefiderocol treatment group and received 2 g, q8h over 3 days. He received a total of 6 infusions (5 complete infusions; the sixth infusion was interrupted due to the patient's death with approximately 25% of the dose administered of cefiderocol) without any Gram-negative adjunctive antibiotics from Day 1 (Screening/Baseline) to Day 3. Before randomization, the patient received 1 dose of colistin and oral vancomycin for 9 days.

On Day 3 (EA), a microbiological laboratory specimen was obtained from the sputum and the culture result was negative. The chest radiograph showed consolidation in both lung fields, right upper lung field with aggravated consolidation of lower left lobe field and right middle lobe field with air-bronchogram was newly developed, and an intact trachea; the lung fields were considered worsened compared to Screening. Arterial blood gases performed with a  $FiO_2$  of 32% showed a  $PaO_2$  of 58 mm Hg,  $PaCO_2$  of 36 mm Hg, and  $SaO_2$  of 79%. No new signs and symptoms were reported, and the dyspnea (including retractions), expectorated sputum production, and rales became severe. The SOFA score was 8, and the CPIS was 6. The inflammatory indices of WBC count, CRP were not improved ( $18.77 \times 10^9/L$ , 20.68 mg/dL, respectively) but the patient had a normal body temperature, 36.1°C. The patient was considered a clinical failure. The patient died on Day 3, after receiving 5 doses of cefiderocol. The sixth infusion of cefiderocol was interrupted due to the patient's death, and approximately 25% of the dose was administered. The cause of death was considered due to aggravated pneumonia by the investigator.

**Table 1 Inflammatory Indices**

Visit	White Blood Cell Count (RR = 4 to 10)	C-reactive Protein (RR = 0 to 0.5)	Body Temperature
Screening/Baseline	$19.63 \times 10^9/L$	17.16 mg/dL	38.1°C
Early Assessment	$18.77 \times 10^9/L$	20.68 mg/dL	36.1°C

RR = reference range

**Table 2 Sequential Organ Failure Assessment and Total Clinical Pulmonary Infection Score Status**

Visit	SOFA Score	Total CPIS
Screening/Baseline	8	5
Early Assessment	8	6

CPIS = Clinical Pulmonary Infection Score; SOFA = Sequential Organ Failure Assessment

**Table 3**                      **Antimicrobial Susceptibility Testing at Screening  
(European Committee on Antimicrobial Susceptibility  
Testing)**

<b>Pathogen</b>	<b>Resistant</b>	<b>Intermediate</b>	<b>Susceptible</b>	<b>Not Applicable</b>
<i>A. baumannii</i>	Amikacin, ciprofloxacin, colistin, imipenem, meropenem	NA	NA	Aztreonam, cefepime, ceftazidime-avibactam, ceftolozane-tazobactam, cefiderocol, tigecycline

NA = not applicable

**Table 4 Susceptibility Testing at Each Visit**

Visit	IHMA Organism ID	AMK	AZT	CFPM	CAZ/ AVI	CEF/ TAZ	CPFX	CST	IPM	MEPM	CFDC	TGC
		MIC µg/mL										
Screening/ Baseline	A. <i>baumannii</i> Sample ID E236117	> 64	32	16	8	4	> 4	> 8	> 64	> 64	0.25	1

AMK = amikacin; AZT = aztreonam; CAZ/AVI = ceftazidime-avibactam; CEF/TAZ = ceftolozane-tazobactam; CFDC = cefiderocol; CFPM = cefepime; CPFX = ciprofloxacin; CST = colistin; ID = identification; IHMA = International Health Management Associates; IPM = imipenem; MEPM = meropenem; MIC = minimum inhibitory concentration; TGC = tigecycline

**Table 5 Chest Radiograph Results**

Visit	Lung Fields/ Airways	Heart/ Vessels	Other Structures	Comparison of Lung Fields to Screening
Screening/ Baseline	Consolidation in both lung fields	NA	NA	NA
Early Assessment	Consolidation in both lung fields, right upper lung field with aggravated consolidation of lower left lobe field and right middle lobe field with air-bronchogram was newly developed, and an intact trachea	NA	NA	Worsened

NA = not applicable

**Table 6 Liver Function Tests**

Visit	AST (RR = 0 to 34)	ALT (RR = 10 to 49)	ALP (RR = 45 to 129)	GGT (RR = 16 to 73)	Total Bilirubin (RR = 0.2 to 1.2)
Screening/Baseline	7 U/L	3 U/L	108 U/L	15 U/L	0.36 mg/dL
Early Assessment	11 U/L	3 U/L	109 U/L	18 U/L	0.27 mg/dL

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase;  
GGT = gamma-glutamyl transferase; RR= reference range

**Table 7 Renal Function Tests**

Visit	Blood Urea Nitrogen (RR = 9 to 23)	Serum Creatinine (RR = 0.7 to 1.3)	Creatinine Clearance
Screening/Baseline	17 mg/dL	1.07 mg/dL	44.78 mL/min
Early Assessment	16 mg/dL	1.16 mg/dL	41.30 mL/min

RR = reference range

**Table 8 Coagulation Tests**

Visit	Platelet Count (RR = 130 to 400)	aPTT (RR = 20 to 38)	PT-INR (RR = 0 to 1)
Screening/Baseline	$337 \times 10^9/L$	54.9 sec	1.90
Early Assessment	$296 \times 10^9/L$	79.9 sec	2.91

aPTT = activated partial thromboplastin time; PT-INR = prothrombin international normalized ratio;  
RR = reference range

### Subject ID Patient # 31

Subject ID	Patient # 31	Country	South Korea			
Age	80	Clinical Diagnosis at Screening	HAP			
Gender	Female	Severity	Moderate			
Race	Asian	APACHE II Score	25			
Height (cm)	160.0	Causative Pathogen at Screening	<i>Acinetobacter baumannii</i> , <i>Klebsiella pneumoniae</i> , <i>Pseudomonas aeruginosa</i>			
Body Weight (kg)	50.3	CR Evidence at Screening (other than central lab)	Positive rapid diagnostic test (chromogenic media)			
MIC of Meropenem	<i>A. baumannii</i> , 1 µg/mL; <i>K. pneumoniae</i> , NA; <i>P. aeruginosa</i> , NA	MIC of Cefiderocol	<i>A. baumannii</i> , 32µg/mL; <i>K. pneumoniae</i> , NA; <i>P. aeruginosa</i> , NA			
MIC of Imipenem	<i>A. baumannii</i> , 1 µg/mL; <i>K. pneumoniae</i> , NA; <i>P. aeruginosa</i> , NA					
Duration of Study Treatment	12 days	Standard of Care	Colistin (75 mg IV)			
Study Drug	Cefiderocol (0.75 g, q12h IV)					
Microbiological Results at TOC		Day 28 All-cause Mortality	Clinical Outcome at TOC			
Persistence (EOT)		Death (Day 13)	Clinical failure (EOT)			
Medical History (Ongoing)	Hypertension; diabetes mellitus; Alzheimer’s dementia; arthrosis; renal cysts, pleural effusion, anemia, chronic kidney disease; fracture of distal tibio-fibula lower leg (right); fracture of (left), osteopenia; left arm cellulitis; ileus; urinary tract infection, several small hepatic cysts, upper GI bleeding, stomatitis, hypocalcemia, hypoalbuminemia; hypophosphatemia, hypokalemia; mild tricuspid regurgitation, pulmonary hypertension (moderate); pitting edema; hypomagnesemia; hypotension					
Medical History (Not Ongoing)	Total knee replacement (both); urinary tract infection; renal abscess; hyperkalemia; open reduction with internal fixation; hyperkalemia; hematemesis, acidosis					
Adverse Event	Day	Severity	Action Taken with Study Drug	Outcome	Causality	Serious
Atrial fibrillation	-1	Moderate	NA (before initial dose of randomized study treatment)	Recovered/ resolved	NA	No
Increased in the left pleural effusion	5	Mild	Dose not changed	Not recovered/ not resolved	Not related	No

Aggravated of upper gastrointestinal bleeding	9	Moderate	Dose not changed	Not recovered/ not resolved	Not related	No
Aggravated pneumonia	10	Severe	Dose not changed	Fatal	Not related	Yes

#### Narrative Summary

An 80-year-old female Asian from South Korea had a medical history of diabetes mellitus, Alzheimer's dementia, chronic kidney disease, and renal abscess.

On Day -79, the patient was admitted for a fracture of the left femur, had osteopenia, underwent open reduction with internal fixation on Day -76, and then was discharged on Day -39.

It was reported that ceftriaxone was provided from Day -24 to Day -22 for left arm cellulitis. On Day -23, the patient developed an ileus. The patient was admitted on Day -22 from an acute care treatment facility to the ICU due to upper GI bleeding (treatment included RBC and platelet transfusion). A urinary tract infection and stomatitis were both reported on Day -22. Piperacillin was given from Day -22 to Day -12 and Day -10 to Day -9; and vancomycin from Day -22 to Day -16. Meropenem was also provided on Day -17. On Day -12, high fever was reported; medication was changed to meropenem, which was provided until Day -11. On Day -11, the diagnosis of HAP was confirmed. On Day -10, piperacillin was provided and on Day -9, colistin was administered. On Day -9, *A. baumannii* (meropenem- and imipenem-resistant) was identified, and vancomycin was provided on the same day. Vancomycin was also provided from Day -7 to Day -1.

On Day -1, Screening was done. The chest x-ray showed haziness in both lungs from Day -22, but aggravated from Day -6. Blood laboratory samples showed an elevated WBC count, and low potassium at 2.8 mmol/L. Sputum culture results showed *A. baumannii*, *K. pneumoniae*, and *P. aeruginosa*.

The patient was randomized into the cefiderocol arm and started the drug on Day 1.

On Day 3, EA was performed. Chest x-ray showed no change in comparison of lung fields to Screening. Blood sample results showed a slightly raised WBC count. Sputum culture identified *A. baumannii* and *P. aeruginosa*. Clinical outcome was clinical failure.

On Day 9, the unrelated moderate AE of aggravated upper GI bleeding was reported and gastric artery embolization was performed on Day 10. Treatment for the SAE of aggravated upper GI bleeding included pantoprazole sodium and packed RBC, platelets, and cryoprecipitate transfusion.

On Day 10, the SAE of aggravated pneumonia was reported. Dose was not changed. On Day 11, she had difficulty breathing, and patient developed aggravated respiratory acidosis. The physician recommended ventilator care, but the patient's son refused. The investigator performed manual resuscitation with bag valve mask and administered vasopressors, but the patient's condition deteriorated. Treatment for the SAE of aggravated pneumonia included acetylcysteine IV and inhalation, ambroxol IV, linezolid IV, budesonide inhalation, hydrocortisone inhalation, ipratropium bromide inhalation, salbutamol inhalation, and sodium bicarbonate IV.

On Day 13, the patient died due to the SAE of aggravated pneumonia. The outcome of the SAE of aggravated pneumonia was Fatal and the investigator considered the event to be not related to study drug.

AE = adverse event; APACHE = Acute Physiology and Chronic Health Evaluation; CR = carbapenem resistance; EA = Early Assessment; EOT = End of Treatment; GI = gastrointestinal; HAP = hospital-acquired pneumonia; ICU = intensive care unit; ID = identification; IV = intravenous; MIC = minimum inhibitory concentration; NA = not available; q12h = every 12 hours; RBC = red blood cell; SAE = serious adverse event; TOC = Test of Cure; unk = unknown; WBC = white blood cell

**Study qualifying diagnosis:** Hospital-acquired pneumonia due to *A. baumannii*, *K. pneumoniae*, and *P. aeruginosa* were identified to be carbapenem resistant through a positive rapid diagnostic test (chromogenic media).

**Study qualifying infection history:** On Day -1, *A. baumannii*, *K. pneumoniae*, and *P. aeruginosa* were identified from the sputum. The isolate containing *A. baumannii* was resistant to amikacin, ciprofloxacin, imipenem, and meropenem, and susceptible to colistin (Table 3).

**Current hospitalization history:** The patient was hospitalized on Day -22 from an acute care treatment facility as an urgent admission into ICU (isolation) due to upper GI bleeding.

**Clinical course:** On Day -1, a microbiological laboratory specimen was obtained from the sputum and WBC polymorphs (3+,  $\geq 25$ , many) and squamous epithelial cells (1+,  $< 10$ , few) were noted. The pathogens *A. baumannii*, *K. pneumoniae*, and *P. aeruginosa* were identified. The chest radiograph showed haziness in both lungs, aggravated since last study, increase in left pleural effusion, and decreased induration of the lungs (Table 5). The arterial blood gases (ABGs) indicated PaO<sub>2</sub> at 77 mm Hg, PaCO<sub>2</sub> at 28 mm Hg, SaO<sub>2</sub> at 95%, and FiO<sub>2</sub> at 28%. The initial clinical assessment of signs and symptoms included moderate fatigue, dyspnea (including retractions), and rales; and severe malaise, cough, expectorated sputum production, and suctioned respiratory secretions. The Sequential Organ Failure Assessment (SOFA) score was 13, and the Clinical Pulmonary Infection Score (CPIS) was 4 (Table 2). The inflammatory indices of WBC count, C- reactive protein (CRP), and body temperature were  $17.38 \times 10^9/L$ , 29.54 mg/dL, and 38.1°C, respectively (Table 1). Urine sample collected showed 2+ for urine occult blood, 3+ urine protein, trace urine urobilinogen, 3+ urine leukocyte esterase, urine sediment WBC was 30 to 49/high power field (HPF) (reference range [RR] 0 to 4), urine RBC was 10 to 19/HPF (RR 0 to 4), with many urine sediment casts.

The patient received her first dose of cefiderocol (0.75 g, q12h, IV) on Day 1 and received 22 subsequent infusions of cefiderocol from Days 2 to 12.

On Day 3 (EA), a microbiological laboratory specimen was obtained from the sputum, and WBC polymorphs (1+,  $< 10$ , few) and squamous epithelial cells (1+,  $< 10$ , few) were noted. The pathogens *A. baumannii* and *P. aeruginosa* were identified. The chest radiograph showed no significant interval change since last study. ABGs indicated PaO<sub>2</sub> at 79 mm Hg, PaCO<sub>2</sub> at 31 mm Hg, SaO<sub>2</sub> at 96%, and FiO<sub>2</sub> at 36%. Signs or symptoms included moderate fatigue, dyspnea (including retractions), and rales, and severe malaise, cough, expectorated sputum production, and suctioned respiratory secretions. The SOFA score was 13, and the CPIS was 5. The inflammatory indices of WBC count, CRP, and body temperature were  $13.10 \times 10^9/L$ , 21.88 mg/dL, and 36.8°C, respectively. The patient was considered a clinical failure.

On Day 5, the patient experienced a mild AE of increase in left pleural effusion, which remained ongoing at the time of death.

On Day 9, the AE of moderate aggravated upper GI bleeding was reported, which remained ongoing at the time of death. Gastric artery embolization was performed on Day 10.

On Day 10, the patient experienced the SAE of severe aggravated of pneumonia. The dose of study medication dosing was not changed. Treatment for the SAE of aggravated pneumonia included acetylcysteine IV and inhalation, ambroxol IV, linezolid IV, budesonide inhalation, hydrocortisone inhalation, ipratropium bromide inhalation, salbutamol inhalation, and sodium bicarbonate IV.

On Day 11 (EOT), a microbiological laboratory specimen was obtained from the sputum, and WBC polymorphs (1+, < 10, few) and squamous epithelial cells (3+, ≥ 25, many) were noted. The pathogens *A. baumannii* and *P. aeruginosa* were identified. The patient had difficulty breathing, and patient went into aggravated respiratory acidosis. The physician recommended ventilator care, but her son refused. The investigator performed manual resuscitation with bag valve mask and administered vasopressors, but her condition deteriorated. The patient had a clinical outcome of indeterminate with microbiological persistence.

On Day 13 (End of Study), the patient died due to the SAE of severe aggravation of pneumonia, 1 day after receiving her last dose of study medication.

The outcome of the SAE of aggravated of pneumonia was Fatal and the investigator considered the event to be not related to study drug.

**Table 1 Inflammatory Indices**

Visit	White Blood Cell Count (RR: 4 to 10)	C-reactive Protein (RR: 0.01 to 0.3)	Body Temperature
Screening/Baseline	$17.38 \times 10^9/L$	29.54 mg/dL	38.1°C
Early Assessment	$13.10 \times 10^9/L$	21.88 mg/dL	36.8°C
End of Study	$13.76 \times 10^9/L$	16.99 mg/dL	37.0°C

RR = reference range

**Table 2 Sequential Organ Failure Assessment and Total Clinical Pulmonary Infection Score Status**

Visit	SOFA Score	Total CPIS
Screening/Baseline	13	4
Early Assessment	13	5

CPIS = Clinical Pulmonary Infection Score; SOFA = Sequential Organ Failure Assessment

**Table 3 Antimicrobial Susceptibility Testing at Screening (European Committee on Antimicrobial Susceptibility Testing)**

Pathogen	Resistant	Intermediate	Susceptible	Not Applicable
<i>Acinetobacter baumannii</i>	Amikacin, ciprofloxacin, imipenem, meropenem	NA	Colistin	Aztreonam, cefepime, ceftazidime-avibactam, ceftolozane-tazobactam, cefiderocol, tigecycline

NA = not available

**Table 4 Susceptibility Testing at Each Visit**

Visit	IHMA Organism ID	AMK	AZT	CFPM	CAZ/ AVI	CEF/ TAZ	CPFX	CST	IPM	MEPM	CFDC	TGC
		MIC µg/mL										
Screening/ Baseline	<i>Acinetobacter baumannii</i> Sample ID E830263	32	> 32	> 16	32	32	> 4	1	32	32	1	1
Early Assessment	<i>Acinetobacter baumannii</i> Sample ID E830280	64	32	> 16	16	32	> 4	1	64	64	0.12	1
Early Assessment	<i>Pseudomonas aeruginosa</i> Sample ID E830269	≤ 4	8	16	4	2	4	1	64	8	0.25	> 4
End of Treatment	<i>Acinetobacter baumannii</i> Sample ID E830273	32	32	> 16	64	> 64	> 4	2	64	64	4	2
End of Treatment	<i>Pseudomonas aeruginosa</i> Sample ID E830278	≤ 4	8	> 16	32	16	0.5	1	8	8	2	2

AMK = amikacin; AZT = aztreonam; CAZ/AVI = ceftazidime-avibactam; CEF/TAZ = ceftolozane-tazobactam; CFDC = cefiderocol; CFPM = cefepime; CPFX = ciprofloxacin; CST = colistin; ID = identification; IHMA = International Health Management Associates; IPM = imipenem; MEPM = meropenem; MIC = minimum inhibitory concentration; TGC = tigecycline

**Table 5 Chest Radiograph Results**

Visit	Lung Fields/ Airways	Heart/ Vessels	Other Structures	Comparison of Lung Fields to Screening
Screening/Baseline	Haziness in both lungs (Day -22); Aggravated since last study (Day -21); Increased in left pleural effusion, decreased induration in lungs (Days -20 to -6)	Aggravated state since last study (Day -5); No significant interval change since last study (Day -4)	Aggravated state since last study (Day -3); Improved but still has haziness in the lungs (Days -2 to -1)	NA
Early Assessment	No significant interval change since last study	NA	NA	No change

NA = not available

**Table 6 Liver Function Tests**

Visit	AST (RR = 8 to 38)	ALT (RR = 4 to 44)	ALP (RR = 35 to 104 )	GGT (RR = 9 to 35)	Total Bilirubin (RR = 0.2 to 1.2)
Screening/Baseline	30 IU/L	7 IU/L	106 IU/L	16 IU/L	1.25 mg/dL
Early Assessment	28 IU/L	11 IU/L	115 IU/L	18 IU/L	1.10 mg/dL
End of Study	29 IU/L	8 IU/L	74 IU/L	NA	1.55 mg/dL

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase;  
GGT = gamma-glutamyl transferase; NA = not available; RR = reference range

**Table 7 Renal Function Tests**

Visit	Blood Urea Nitrogen (RR = 8 to 22)	Serum Creatinine (RR = 0.5 to 0.9)	Creatinine Clearance
Screening/Baseline	21.7 mg/dL	1.99 mg/dL	17.90 mL/min
Early Assessment	8.4 mg/dL	0.99 mg/dL	35.98 mL/min
End of Study	11.9 mg/dL	1.41 mg/dL	NA

NA = not available; RR = reference range

**Table 8 Coagulation Tests**

Visit	Platelet Count (RR = 140 to 400)	aPTT (RR = 29 to 45)	PT-INR (RR = 0.87 to 1.2)
Screening/Baseline	$247 \times 10^9/L$	53.9 sec	1.35
Early Assessment	$94 \times 10^9/L$	49.4 sec	1.36
End of Study	$36 \times 10^9/L$	50.0 sec	1.19

aPTT = activated partial thromboplastin time; PT-INR = prothrombin international normalized ratio;  
RR = reference range

## Subject ID Patient # 32

Subject ID	Patient # 32	Country	Thailand			
Age	84	Clinical Diagnosis at Screening	VAP			
Gender	Female	Severity	Severe			
Race	Asian	APACHE II Score	22			
Height (cm)	150.0	Causative Pathogen at Screening	Stenotrophomonas maltophilia			
Body Weight (kg)	30.0	CR Evidence at Screening (other than central lab)	Treatment failure CR-GNB			
MIC of Meropenem	> 64 µg/mL	MIC of Cefiderocol	0.06 µg/mL			
MIC of Imipenem	> 64 µg/mL					
Duration of Study Treatment	14 days	Standard of Care	Colistin (150 mg IV) Amikacin (500 mg IV) Levofloxacin (500 mg IV)			
Study Drug Treatment	Cefiderocol (1, 1.5 g q8h IV)					
Microbiological Results at TOC		Day 28 All-cause Mortality			Clinical Outcome at TOC	
Microbiological persistence (EOT)		Death ( Day 15)			Clinical Failure (EOT)	
Medical History (Ongoing)	Hypertension; thoracic aortic aneurysm s/p TEVAR; paraplegia, lumbar spondylosis; stroke-lacunar infarction right internal capsule; oliguria; infected bed sore, acute kidney injury; metabolic acidosis; hyperlipidemia; hypocalcemia; hypokalemia; anemia, constipation; rectal ulcer; hypomagnesemia; bronchospasm; UTI					
Medical History (Not Ongoing)	HAP; hyperkalemia; hypernatremia; lower GI bleeding from rectal ulcer					
Adverse Event	Day	Severity	Action Taken with Study Drug	Outcome	Causality	Serious
Hypotension	1	Moderate	(no data)	Recovered/resolved	(no data)	No
Worsening hypomagnesemia	1	Moderate	Dose not changed	Recovered/resolved	Not related	No
Diarrhea	5	Moderate	Dose not changed	Not recovered/not resolved	Not related	No
Enterococcus faecium UTI	6	Moderate	Dose not changed	Recovered/resolved	Not related	No
Adrenal insufficiency	9	Moderate	Dose not changed	Not recovered/not resolved	Not related	No
Septic shock	9	Severe	Dose not changed	Fatal	Not related	Yes
VRE	13	Moderate	Dose not changed	Not recovered/not resolved	Not related	No

Hypoalbuminemia	14	Moderate	Dose not changed	Not recovered/ not resolved	Not related	No
Cardiac arrest	15	Severe	Not applicable	Fatal	Not related	Yes

#### Narrative Summary

An 84-year-old Asian female from Thailand had a medical history of hypertension and thoracic aortic aneurysm s/p TEVAR.

On Day -30, the patient was hospitalized from an acute care treatment facility to the general ward due to fatigue of both legs causing inability to walk. Lumbar spondylosis with cord compression was suspected. On Day -28, HAP was reported due to a high fever and suspected sepsis. Empiric treatment was initiated. She became “drowsy,” and a CT scan showed a stroke (lacunar infarction right internal capsule). The patient was intubated and placed on mechanical ventilation. On Day -21, the patient had a fever and VAP was suspected. Clindamycin was administered and then changed to meropenem.

On Day -18, the patient was transferred to an acute care treatment facility (bed availability) as she was still receiving meropenem until Day -6. On Day -16, she was transferred to ICU. Treatment included meropenem and amikacin, and the patient’s condition improved. The patient was extubated and removed from mechanical ventilation on Day -11. It was reported that the patient had wheezing, was re-intubated and placed back on mechanical ventilation on Day -9. On Day -8, the patient experienced lower GI bleeding from a rectal ulcer (until Day -5). Omeprazole was provided as treatment. Meropenem was discontinued on Day -4, but was given again from Day -3 to Day 1. Amikacin was given until Day 1, and colistin was administered from Day -10 to Day 1.

It was reported that on Day -4, the patient had developed a high fever, increase of respiratory secretions, and had worsening of respiratory rate with increased lung infiltration. On Day 1, Screening/Baseline, the patient was diagnosed with VAP. Chest x-ray showed localized alveolar infiltration combined with interstitial infiltration and bronchiectasis at LLL and pneumonia with bronchiectasis at RLL. Sputum culture obtained identified *S. maltophilia*. On Day 1, she was randomized to the cefiderocol group. Treatment with cefiderocol 1.5 g q8h IV was initiated on Day 1. The dose was adjusted to 1 g q8h IV on Day 4 as eGFR decreased from 36 mL/min/1.73m<sup>2</sup> to 28 mL/min/1.73m<sup>2</sup>. It was adjusted back to 1.5 g q8h IV on Day 7 to Day 13 as eGFR rose from 28 mL/min/1.73m<sup>2</sup> to 32 mL/min/1.73m<sup>2</sup>. On Day 13 to Day 14, cefiderocol was adjusted again to 1 g q8h as eGFR decreased from 32 mL/min/1.73m<sup>2</sup> to 26 mL/min/1.73m<sup>2</sup>.

On Day 3, EA, chest x-ray showed improvement. Sputum culture obtained was negative. The patient was considered a clinical cure. The unrelated moderate AE of diarrhea was reported on Day 5. Treatment was provided with metronidazole.

On Day 6, Unscheduled Visit, urine culture (mid-stream clean catch) and bed sore swab culture obtained identified *E. faecium*. The unrelated moderate AE *E. faecium* UTI was reported. Treatment included vancomycin.

On Day 9, Unscheduled Visit, *A. baumannii* and *S. maltophilia* were isolated from the sputum culture, and coagulase-positive *Staphylococci* and *E. faecium* were isolated from the bed sore swab culture. On the same day (Day 9), the unrelated SAE septic shock was reported. Norepinephrine was initiated. Septic work up was performed; blood culture obtained was negative and sputum cultures obtained detected Gram-positive cocci.

On Day 13, Unscheduled Visit, the AE *E. faecium* UTI was reported recovered/resolved. TA culture obtained identified *Enterococcus*, *K. pneumoniae*, and *S. maltophilia*. The unrelated moderate AE VRE pneumonia was reported. Treatment was provided with linezolid.

On Day 14, EOT, chest x-ray showed no change. *K. pneumoniae* and *S. maltophilia* were detected from the sputum culture. The patient was considered a clinical failure with microbiological persistence.

On Day 15, the unrelated SAE of cardiac arrest was reported at 09:30 hours. CPR was started with treatment and after 5 minutes; ECG showed sinus tachycardia. The patient was unstable, monitored, and expired at 10:05 hours. The patient died due to cardiac arrest and septic shock.

AE = adverse event; APACHE =Acute Physiology and Chronic Health Evaluation;

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CPR = cardiopulmonary resuscitation; CR = carbapenem resistance; CT = computed tomography; EA = Early Assessment; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EOT = End of Treatment; GI = gastrointestinal; GNB = Gram-negative bacteria; HAP = hospital-acquired pneumonia; ICU = intensive care unit; ID = identification; IV = intravenous; LLL = left lower lobe; MIC = minimum inhibitory concentration; q8h = every 8 hours; RLL = right lower lobe; SAE = serious adverse event; s/p = status post; TA = tracheal aspirate; TEVAR = thoracic endovascular aortic repair; TOC = Test of Cure; unk = unknown; UTI = urinary tract infection; VAP = ventilator-acquired pneumonia; VRE = vancomycin-resistant *Enterococci*

**Study qualifying diagnosis:** Ventilator-associated pneumonia due to *S. maltophilia* with evidence of carbapenem resistance through treatment failure CR-GNB.

**Study qualifying infection history:** At Screening/Baseline, *S. maltophilia* was identified from sputum and showed not applicable to all anti-infectives that were tested (Table 3).

**Current hospitalization history:** The patient was admitted from an acute care treatment facility on Day -30 onto a general ward in a hospital due to fatigue of both legs. On Day -28, she became drowsy, and a brain CT scan was taken, which demonstrated lacunar infarction and a stroke. On the same day, she developed HAP and was intubated. After that, she had high fever, and because sepsis was suspected, empiric treatment was started. Her condition improved on Day -28.

On Day -18, the subject was transferred to a second hospital, and then, on Day -16, was admitted to the site hospital. On admission to the site, the subject was started on treatment with meropenem. On Day -9, she was started on ventilation again with continuous mandatory ventilation.

The patient received colistin (100/150/300 mg) on Day-10 through Day 1 and amikacin on Day 1 for the treatment of VAP. Meropenem was administered on Day -3 to Day 1. The patient's sputum sampled on Day 1 grew *S. maltophilia*; therefore, the patient was enrolled in this study.

**Clinical course:** On Day 1 (Screening/Baseline), a microbiological laboratory specimen was obtained from the sputum, and white blood cell (WBC) polymorphs (2+, 10 to 24, moderate) and squamous epithelial cells (1+, < 10, few) were noted. Gram negative rods were not identified. The pathogen *S. maltophilia* (no quantification, light growth) was identified. A chest radiograph showed localized alveolar infiltration combined with interstitial infiltration at left lower lobe and interstitial infiltration with bronchiectasis at left lower lobe and pneumonia with bronchiectasis at right lower lobe (Table 5). The patient was on a ventilator. Arterial blood gases (ABGs) showed PaO<sub>2</sub> 160 mm Hg, PaCO<sub>2</sub> 31 mm Hg, SaO<sub>2</sub> 100%, and FiO<sub>2</sub> 40%. Signs and symptoms at the initial clinical assessment included moderate fatigue, malaise, cough, dyspnea (including retractions), suctioned respiratory secretions, rales, rhonchi, dullness on percussion, and mild bronchial breath sounds. ECG results showed an abnormal ECG rate (109 beats per minute). The Sequential Organ Failure Assessment (SOFA) score was 2 and the Clinical Pulmonary Infection Score Status (CPIS) was 5 (Table 2). The inflammatory indices of WBC count, C-reactive protein (CRP), and body temperature were  $17.2 \times 10^9/L$ , 80.6 mg/L, and 39.2°C, respectively (Table 1).

Treatment with cefiderocol (1.5 g, q8h IV) was initiated on Day 1 (blood urea nitrogen was 43.4 mg/dL, creatinine was 1.47 mg/dL). The patient received 7 subsequent infusions of cefiderocol (1.5 g q8h). The dose of cefiderocol was adjusted to 1 g q8h due to elevated creatinine beginning on Day 4. She received 9 infusions at this dose through Day 7. The dose of cefiderocol was changed to 1.5 g q8h on Day 7 through Day 13 and then 1 g q8h on the same day through Day 14. She received a total of 39 infusions of cefiderocol.

On Day 3 (EA), a microbiological laboratory specimen was obtained from the sputum, and WBC polymorphs (1+, < 10, few) and squamous epithelial cells (1+, < 10, few) were noted. A chest radiograph showed improved pneumonia at left lower lobe; unchanged pneumonia with bronchiectasis at right lower lobe. The patient was on a ventilator. Arterial blood gases showed PaO<sub>2</sub> 182 mm Hg, PaCO<sub>2</sub> 35 mm Hg, SaO<sub>2</sub> 100%, and FiO<sub>2</sub> 40%. No new signs and symptoms were reported, and there was an improvement in dullness on percussion, dyspnea (including retractions), rales, rhonchi, and suctioned respiratory secretions. The SOFA score was 1, and the CPIS was 2. The inflammatory indices of WBC count, CRP, and body temperature were  $18.90 \times 10^9/L$ , 113.2 mg/L, and 37.0° C, respectively. The patient was considered a clinical cure.

On Day 6, a microbiological laboratory specimen was obtained from the urine (mid-stream clean catch). The pathogen *E. faecium* (quantitation,  $> 1 \times 10^5$ ) was identified. Another microbiological laboratory specimen was obtained from the bed sore swab. The pathogen *E. faecium* (no quantitation, moderate growth) was identified. The patient experienced an *E. faecium* UTI. Vancomycin (600 mg/1000 mg IV) was administered on Day 6.

On Day 9 (Unscheduled Visit), a microbiological laboratory specimen was obtained from the bed sore swab. The pathogen *E. faecium* (no quantitation, light growth) was identified. Another microbiological laboratory specimen was obtained from the sputum and WBC polymorphs (3+,  $\geq 25$ , many) and squamous epithelial cells (1+, < 10, few) were noted. Gram-negative rods (+) were identified. The pathogens *Coagulase positive staphylococcus* (no quantitation, light growth), *E. faecium* (no quantitation, light growth), *A. baumannii* (no quantitation, moderate growth), and *S. maltophilia* (no quantitation, moderate growth) were identified.

The patient developed an AE of adrenal insufficiency and an SAE of septic shock on Day 9. The patient received hydrocortisone, norepinephrine, and prednisolone for treatment.

On Day 13, a microbiological laboratory specimen was obtained from the TA, and WBC polymorphs (2+, 10 to 24, moderate) and squamous epithelial cells (2+, 10 to 24, moderate) were noted. Gram-negative rods (2+) were identified. The pathogens *Enterococcus* (no quantitation, moderate growth), *K. pneumoniae* (no quantitation, moderate growth), and *S. maltophilia* (no quantitation, moderate growth) were identified. For an AE of VRE pneumonia (moderate), linezolid was started.

On Day 14, (EOT) a microbiological laboratory specimen was obtained from the sputum. Gram-negative rods were identified (3+). The pathogens *Klebsiella pneumoniae* and *S. maltophilia* (quantification not reported for either pathogen) were identified. A chest radiograph demonstrated minimally improved interstitial infiltration at left lower lung field, and increased haziness at right lower lung field. There was no improvement compared to Screening. PaO<sub>2</sub> was 162 mm Hg, PaCO<sub>2</sub> was 28 mm Hg, SaO<sub>2</sub> was 100%, FiO<sub>2</sub> was 60%. No new signs and symptoms were reported and there were improvements in cough, dyspnea (including retractions), fatigue and malaise. The SOFA score was 8 and CPIS was 3. The inflammatory indices of WBC count, CRP, and body temperature were  $50.8 \times 10^9/L$ , 23.9 mg/L, and 37.0°C, respectively. The patient was considered a clinical failure with microbiological persistence

The patient died on Day 15 due to the SAEs of cardiac arrest and septic shock, 1 day after receiving her last dose of study drug. The SAEs were both severe and not considered to be related to study drug.

**Table 1 Inflammatory Indices**

Visit	White Blood Cell Count (RR = 4.6 to 10.6)	C-reactive Protein (RR = 0 to 3)	Body Temperature
Screening/Baseline	$17.2 \times 10^9/L$	80.6 mg/L	39.2°C
Early Assessment	$18.90 \times 10^9/L$	113.2 mg/L	37.0°C
End of Treatment	$50.8 \times 10^9/L$	23.9 mg/L	37.0°C

RR = reference range

**Table 2 Sequential Organ Failure Assessment and Total Clinical Pulmonary Infection Score Status**

Visit	SOFA Score	Total CPIS
Screening/Baseline	2	5
Early Assessment	1	2
End of Treatment	8	3

CPIS = Clinical Pulmonary Infection Score; SOFA = Sequential Organ Failure Assessment

**Table 3 Antimicrobial Susceptibility Testing at Screening (European Committee on Antimicrobial Susceptibility Testing)**

Pathogen	Resistant	Intermediate	Susceptible	Not Applicable
<i>Stenotrophomonas maltophilia</i>	NA	NA	NA	Amikacin, aztreonam, cefepime, ceftazidime-avibactam, ceftolozane-tazobactam, ciprofloxacin, colistin, imipenem, meropenem, cefiderocol, tigecycline

NA = not applicable

**Table 4 Susceptibility Testing at Each Visit**

Visit	IHMA Organism ID	AMK	AZT	CFPM	CAZ/AVI	CEF/TAZ	CPFX	CST	IPM	MEPM	CFDC	TGC
		MIC µg/mL										
Screening/ Baseline	<i>Stenotrophomonas maltophilia</i> Sample ID E140288	64	> 32	> 16	64	> 64	4	2	> 64	> 64	0.06	1
End of Treatment	<i>Stenotrophomonas maltophilia</i> Sample ID E140285	64	> 32	> 16	64	64	> 4	4	> 64	> 64	0.25	1

AMK = amikacin; AZT = aztreonam; CAZ/AVI = ceftazidime-avibactam; CEF/TAZ = ceftolozane-tazobactam; CFDC = cefiderocol; CFPM = cefepime; CPFX = ciprofloxacin; CST = colistin; ID = identification; IHMA = International Health Management Associates; IPM = imipenem; MEPM = meropenem; MIC = minimum inhibitory concentration; TGC = tigecycline

**Table 5 Chest Radiograph Results**

Visit	Lung Fields/ Airways	Heart/ Vessels	Other Structures	Comparison of Lung Fields to Screening
Screening/ Baseline	Localized alveolar infiltration combined with interstitial infiltration at LLL is seen. Interstitial infiltration with bronchiectasis at LLL is seen; pneumonia with bronchiectasis at RLL.	The heart size appears normal	Degenerative changes of the spine	NA
Early Assessment	Improved pneumonia at LLL; unchanged pneumonia with bronchiectasis at RLL	The heart size appears normal	Degenerative changes of the spine	Improved
End of Treatment	Minimal improved interstitial infiltration at left lower lung field. Increased haziness at right lower lung field	The heart size appears normal	NA	No change

LLL = left lower lobe; NA = not applicable; RLL = right lower lobe

**Table 6 Liver Function Tests**

Visit	AST (RR = 12 to 32)	ALT (RR = 4 to 36)	ALP (RR = 42 to 121)	GGT (RR = 0 to 50)	Total Bilirubin (RR = 0.3 to 1.5)
Screening/Baseline	30 U/L	21 U/L	90 U/L	NA	0.9 mg/dL
Early Assessment	35 U/L	25 U/L	111 U/L	26 U/L	0.6 mg/dL
End of Treatment	32 U/L	13 U/L	102 U/L	43 U/L	0.4 mg/dL

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyl transferase; NA = not available; RR = reference range

**Table 7 Renal Function Tests**

Visit	Blood Urea Nitrogen (RR = 5.8 to 19.1)	Serum Creatinine (RR = 0.5 to 1.5)	Creatinine Clearance
Screening/Baseline	43.4 mg/dL	1.47 mg/dL	13.49 mL/min
Early Assessment	41 mg/dL	1.66 mg/dL	11.95 mL/min
End of Treatment	62.6 mg/dL	2.29 mg/dL	8.66 mL/min

RR = reference range

**Table 8 Coagulation Tests**

Visit	Platelet Count (RR = 173 to 383)	aPTT (RR = 26.06 to 37.01)	PT-INR (RR = 0.89 to 1.31)
Screening/Baseline	$133 \times 10^9/L$	41.5 sec	1.69
Early Assessment	$163 \times 10^9/L$	43.2 sec	1.55
End of Treatment	$133 \times 10^9/L$	53.7 sec	2.8

aPTT = activated partial thromboplastin time; PT-INR = prothrombin international normalized ratio; RR = reference range

### Subject ID Patient # 33

Subject ID	Patient # 33	Country	Republic of Korea			
Age	73	Clinical Diagnosis at Screening	HAP			
Gender	Male	Severity	Moderate			
Race	Asian	APACHE II Score	18			
Height (cm)	171	Causative Pathogen at Screening	Acinetobacter baumannii			
Body Weight (kg)	51	CR Evidence at Screening (other than central lab)	Treatment failure CR-GNB (chromogenic media)			
MIC of Meropenem	A. baumannii, 64 µg/mL; MRSA, 64 µg/mL	MIC of Cefiderocol	A. baumannii, 0.12 µg/mL; MRSA, NA			
MIC of Imipenem	A. baumannii, 64 µg/mL; MRSA, > 64 µg/mL					
Duration of Study Treatment	14 days	Standard of Care	Ciprofloxacin 400 mg IV			
Study Drug	Cefiderocol 1 g to 1.5 g q8h IV					
Microbiological Results at TOC		Day 28 All-cause Mortality		Clinical Outcome at TOC		
Microbiological persistence		Alive (Death on Day 37)		Clinical failure		
Medical History (Ongoing)	Cerebrovascular accident; pneumoconiosis, diabetes mellitus, hypertension; acute intestinal infarction, hepatitis					
Medical History (Not Ongoing)	Cataract surgery , colon cancer, right femur fracture, depression					
Adverse Event	Day	Severity	Action Taken with Study Drug	Outcome	Causality	Serious
Increased AST	4	Severe	Dose not changed	Recovered/ resolved	Related	No
Increased ALT	4	Severe	Dose not changed	Recovered/ resolved	Related	No
Diarrhea	6	Moderate	Dose not changed	Recovered/ resolved	Not related	No
Fever	8	Moderate	Dose not changed	Recovered/ resolved	Not related	No
Fever	24	Mild	Not applicable	Recovered/ resolved	Not related	No
Fever	28	Moderate	Not applicable	Recovered/ resolved	Not related	No
Heart rate elevation	28	Moderate	Not applicable	Recovered/ resolved	Not related	No
Fever	34	Mild	Not applicable	Recovered/ resolved	Not related	No

Pneumonia	37	Severe	Not applicable	Fatal	Not related	Yes
<b>Narrative Summary</b>						
<p>A 73-year-old Asian male from South Korea had a medical history of colon cancer, cerebrovascular accident, right femur fracture, pneumoconiosis, hypertension, and diabetes mellitus.</p> <p>On Day -25, the patient was admitted to the ICU from home due to an acute intestinal infarction and underwent a segmental resection of the ileum and endo-ileostomy. On the same day (Day -25), hepatitis was reported and the patient was placed on mechanical ventilation until Day -14. Treatment included metronidazole (Day -20 to Day -3), meropenem (Day -16 to Day -2), and cefoperazone-sulbactam (Day -2 to Day 1).</p> <p>On Day -1, sputum culture obtained identified <i>A. baumannii</i> and <i>Streptococcus viridans</i>.</p> <p>On Day 1, Screening/Baseline, the patient was diagnosed with HAP (onset date of infection Day -3). Chest x-ray showed bilateral consolidation, "haziness." Sputum culture identified <i>A. baumannii</i> and MRSA. A rapid diagnostic test with chromogenic media demonstrated evidence of carbapenem resistant Gram-negative rods. He was randomized to the cefiderocol arm and received cefiderocol 1.5 g q8h IV on Day 1 to Day 8.</p> <p>Ciprofloxacin and teicoplanin were provided as adjunctive therapy.</p> <p>On Day 4 EA, chest x-ray showed improvement. Sputum culture obtained identified MRSA. Blood laboratory tests showed high AST of 307 U/L and ALT of 154 U/L. The severe related AEs of increased AST and increased ALT were reported. Silybum marianum and penna were provided as treatment. The clinical outcome was considered a clinical failure.</p> <p>On Day 6, the patient experienced the moderate unrelated AE of diarrhea. Metronidazole was provided as treatment.</p> <p>On Day 8, Unscheduled Visit, the dose of cefiderocol was reduced to 1 g q8h to Day 14 due to creatinine clearance (values not reported). On Day 11, blood laboratory results showed AST of 28 U/L and ALT of 30. The AEs of increased AST and increased ALT were considered recovered/resolved. The investigator considered the liver-related events related to the study drug.</p> <p>On Day 14, EOT, chest x-ray showed improvement. Sputum culture obtained identified MRSA. The clinical outcome was considered a clinical cure with microbiological eradication.</p> <p>Linezolid was administered from Days 19 to 32.</p> <p>On Day 20, TOC, chest x-ray showed no change. Sputum culture obtained identified MRSA, <i>A. baumannii</i>, and <i>Proteus mirabilis</i>. The clinical outcome was considered a clinical failure with microbiological persistence.</p> <p>On Day 26, Follow-up, chest x-ray showed no changes. Sputum culture obtained identified <i>A. baumannii</i> and <i>P. mirabilis</i>. His clinical outcome was clinical failure, and his microbiological outcome was reported as microbiological persistence. Cefoperazone-sulbactam was started, and metronidazole was also started on Day 28. The investigator recommended performing a tracheal resection but the patient's family declined. Linezolid and cefoperazone-sulbactam were completed on Day 32. On Day 33, levofloxacin, ampicillin-sulbactam, and doxycycline were started as prophylaxis for infection.</p> <p>On Day 37, the SAE of pneumonia was reported. The patient experienced a cardiac arrest and expired at 6:40 hours, on Day 37. It was reported he had no pupillary reflex, no carotid and radial pulse. The investigator considered that the worsening of pneumonia was due to <i>A. baumannii</i> or <i>P. mirabilis</i> and the death unrelated to cefiderocol.</p>						

AE = adverse event; ALT = alanine aminotransferase; APACHE = Acute Physiology and Chronic Health Evaluation; AST = aspartate aminotransferase; CR = carbapenem resistance/resistant; EA = Early Assessment; EOT = End of Treatment; GNB = Gram-negative bacteria; HAP = hospital-acquired pneumonia; ICU = intensive care unit; ID = identification; IV = intravenous; MIC = minimum inhibitory concentration; MRSA = methicillin-resistant *Staphylococcus aureus*; NA = not available; q8h = every 8 hours; SAE = serious adverse event; TOC = Test of Cure; unk = unknown

**Study qualifying diagnosis:** Hospital-acquired pneumonia due to *A. baumannii* identified to be CR through treatment failure (chromogenic media)

**Study qualifying infection history:** On Day 1, *A. baumannii* resistant to amikacin, ciprofloxacin, imipenem, and meropenem was identified from the sputum. The isolate was susceptible to colistin (Table 3). The isolate *S. aureus* (MRSA) resistant to ciprofloxacin was identified from the sputum.

In parallel with the identification, the patient received ciprofloxacin from Day 1 to Day 14, cefoperazone-sulbactam on Days -2 to 1; and teicoplanin on Days 6 to 13.

**Current hospitalization history:** The patient was hospitalized from home as an emergency admission due to acute intestinal infarction and was admitted to the ICU on (Day -24). The onset date of the HAP infection was Day -17. Ventilation (unknown method) was provided from Days -25 to -14.

**Clinical course:** On Day -1, a microbiological laboratory specimen was obtained from the sputum, and white blood cell (WBC) polymorphs (3+,  $\geq 25$ , many) and squamous epithelial cells (1+,  $< 10$ , few) were noted. Gram-negative rods (+) were noted. The pathogens *A. baumannii* (no quantitation, heavy growth) and *Streptococcus viridans* (no quantitation, moderate growth) were identified.

On Day 1 (Screening/Baseline), a microbiological laboratory specimen was obtained from the sputum, and WBC polymorphs (3+,  $\geq 25$ , many) and squamous epithelial cells (2+, 10 to 24, moderate) were noted. Gram-negative rods (+/-) were identified. The pathogens *A. baumannii* (no quantitation, light growth) and *S. aureus* (MRSA, no quantitation, moderate growth) were identified. The chest radiograph showed consolidation and haziness in both lungs (Table 5). Arterial blood gases (ABGs) showed PaO<sub>2</sub> 154 mm Hg, PaCO<sub>2</sub> 33 mm Hg, SaO<sub>2</sub> 99%, and FiO<sub>2</sub> 30%. The initial clinical assessment of signs and symptoms was performed and revealed moderate dyspnea (including retractions), suctioned respiratory secretions, wheezing, and rales. The Sequential Organ Failure Assessment (SOFA) score was 3, and the Clinical Pulmonary Infection Score (CPIS) was 3 (Table 2). The inflammatory indices of WBC count, C-reactive protein (CRP), and body temperature were  $10.77 \times 10^9/L$ , 9.90 mg/dL, and 37.5°C, respectively (Table 1).

The patient received his first dose of cefiderocol 1.5 g q8h on Day 1. He received 20 subsequent doses of cefiderocol 1.5 g q8h on Days 1 through 8. The dose of cefiderocol was reduced to 1 g q8h on Days 8 through 14 due to renal function (creatinine clearance), and the patient received 18 additional doses.

On Day 4 (EA), a microbiological laboratory specimen was obtained from the sputum, and WBC polymorphs (3+,  $\geq 25$ , many) and squamous epithelial cells (2+, 10 to 24, moderate) were noted. Gram-negative rods (+/-) were identified. The pathogen MRSA (no quantitation, heavy growth) was identified, but the pathogen *A. baumannii* was not identified. The chest radiograph showed a slight improvement of the haziness in both lungs, specifically, in the left lower lung field. The ABGs showed PaO<sub>2</sub> 99 mm Hg,

PaCO<sub>2</sub> 32 mm Hg, SaO<sub>2</sub> 98%, and FiO<sub>2</sub> 30%. No new signs or symptoms were noted. The SOFA score was 4, and the CPIS was 4. The inflammatory indices of WBC count, CRP, and body temperature were  $11.62 \times 10^9/L$ , 4.71 mg/dL, and 37.5°C, respectively. The clinical outcome was considered as a clinical failure.

The patient experienced AEs of increased AST 307 U/L (reference range [RR] = 0 to 40) and increased ALT 154 U/L (RR = 0 to 40) on Day 4. The study medication dose was not changed, and Legalon (silybum marianum; milk-thistle fruit extract powder [silymarin 0.14 g, silybin 60 mg] 0.3394 g) and Pennel (diphenyl dimethyl dicarboxylate 25 mg/garlic oil 50 mg) were administered from Day 4 to Day 11 as treatment. The investigator considered the events severe and related to the study drug. Total bilirubin was not elevated at 1.14 mg/dL.

On Day 8, the dose of cefiderocol was reduced to 1 g q8h due to renal function.

From Days 9 to 18, oral metronidazole also was administered for the treatment of diarrhea that occurred on Day 6. The hepatic AEs resolved on Day 11.

On Day 14 (EOT), a microbiological laboratory specimen was obtained from the sputum, and WBC polymorphs (1+, < 10, few) and squamous epithelial cells (3+, ≥ 25, many) were noted. The pathogen *A. baumannii* was not identified, but *S. aureus* (MRSA, no quantitation, moderate growth) was identified. The chest radiograph was improved compared to baseline and showed haziness on the right lower lung field, probably pleural effusion. The ABGs showed PaO<sub>2</sub> 161 mm Hg, PaCO<sub>2</sub> 30 mm Hg, SaO<sub>2</sub> 99%, and FiO<sub>2</sub> 28%. Signs and symptoms included mild dyspnea, suctioned respiratory secretions, wheezing, and rales. The SOFA score was 3, and the CPIS was 2. The inflammatory indices of WBC count, CRP, and body temperature were  $7.01 \times 10^9/L$ , 4.44 mg/dL, and 37.1°C, respectively. AST and ALT levels were 20 U/L and 12 U/L, respectively. The clinical outcome was considered a clinical cure with microbiological eradication. The diarrhea resolved on Day 18 and was considered not related to study drug.

On Day 20 (TOC), a microbiological laboratory specimen was obtained from the sputum, and WBC polymorphs (2+, 10 to 24, moderate) and squamous epithelial cells (3+, ≥ 25, many) were noted. Gram-negative rods (+) were identified. The pathogens *S. aureus* (MRSA, no quantitation, moderate growth), *A. baumannii* (no quantitation, moderate growth), and *P. mirabilis* (no quantitation, light growth) were identified. The chest radiograph showed no change compared to baseline; marked consolidation and haziness in both lungs. The ABGs showed PaO<sub>2</sub> 75 mm Hg, PaCO<sub>2</sub> 32 mm Hg, SaO<sub>2</sub> 96%, and FiO<sub>2</sub> 24%. Signs and symptoms included mild dyspnea, wheezing, and rales and moderate suctioned respiratory secretions. The SOFA score was 4, and the CPIS was 3. The inflammatory indices of WBC count, CRP, and body temperature were  $10.22 \times 10^9/L$ , 2.55 mg/dL, and 36.7°C, respectively. The clinical outcome was considered a clinical failure with microbiological persistence.

On Day 26 (Follow-up), a microbiological laboratory specimen was obtained from the sputum, and WBC polymorphs (3+, ≥ 25, many) and squamous epithelial cells (1+, < 10, few) were noted. Gram-negative rods (+-) were identified. The pathogens *A. baumannii*

(no quantitation, moderate growth) and *P. mirabilis* (no quantitation, light growth) were identified. The chest radiograph showed no change compared to baseline; marked consolidation and haziness in both lungs. The ABGs showed PaO<sub>2</sub> at 104 mm Hg, PaCO<sub>2</sub> at 34 mm Hg, SaO<sub>2</sub> at 98%, and FiO<sub>2</sub> at 28%. Signs and symptoms included mild dyspnea, wheezing and rales; and moderate suctioned respiratory secretions. The SOFA score was 3, and the CPIS was 4. The inflammatory indices of WBC count, CRP, and body temperature were  $13.15 \times 10^9/L$ , 5.25 mg/dL, and 36.7°C, respectively. The clinical outcome was considered a clinical failure with microbiological persistence.

The patient's family declined to have a tracheal resection performed on the patient, even though it was recommended by the investigator to keep the patient breathing.

Cefoperazone-sulbactam was started from Day 26, and metronidazole was started from Day 28. Linezolid was administered until Day 32 and cefoperazone-sulbactam was completed on Day 33. On Day 33, levofloxacin, ampicillin-sulbactam, and doxycycline were started for prophylaxis of infection.

On Day 37, the patient died due to the SAE of pneumonia. The investigator considered that the cause of pneumonia was due to *A. baumannii* or *P. mirabilis*. The investigator considered the death unrelated to cefiderocol.

**Table 1 Inflammatory Indices**

Visit	White Blood Cell Count (RR = 4 to 10)	C-reactive Protein (RR = 0 to 0.3)	Body Temperature
Screening/Baseline	$10.77 \times 10^9/L$	9.90 mg/dL	37.5°C
Early Assessment	$11.62 \times 10^9/L$	4.71 mg/dL	37.5°C
End of Treatment	$7.01 \times 10^9/L$	4.44 mg/dL	37.1°C
Test of Cure	$10.22 \times 10^9/L$	2.55 mg/dL	36.7°C
Follow-up	$13.15 \times 10^9/L$	5.25 mg/dL	36.7°C

RR = reference range

**Table 2 Sequential Organ Failure Assessment and Total Clinical Pulmonary Infection Score Status**

Visit	SOFA Score	Total CPIS
Screening/Baseline	3	3
Early Assessment	4	4
End of Treatment	3	2
Test of Cure	4	3
Follow-up	3	4

CPIS = Clinical Pulmonary Infection Score; SOFA = Sequential Organ Failure Assessment

**Table 3                      Antimicrobial Susceptibility Testing at Screening  
(European Committee on Antimicrobial Susceptibility  
Testing)**

Pathogen	Resistant	Intermediate	Susceptible	Not Applicable
<i>Acinetobacter baumannii</i>	Amikacin, ciprofloxacin, imipenem, meropenem	NA	Colistin	Aztreonam, ceftazidime-avibactam, ceftolozane-tazobactam, cefiderocol, tigecycline, cefepime
Methicillin-resistant <i>Staphylococcus aureus</i> (MRSA)	Ciprofloxacin	NA	NA	Cefepime, imipenem, meropenem,

NA = not available

**Table 4 Susceptibility Testing at Each Visit**

Visit	IHMA Organism ID	AMK	AZT	CFPM	CAZ/ AVI	CEF/ TAZ	CPFX	CST	IPM	MEPM	CFDC	TGC
		MIC µg/mL										
Screening/ Baseline	<i>Acinetobacter baumannii</i> Sample ID E725930	> 64	32	> 16	16	16	> 4	1	64	64	0.12	1
Test of Cure	<i>Acinetobacter baumannii</i> Sample ID E797587	> 64	32	> 16	16	8	> 4	> 8	64	64	0.06	1
Follow-up	<i>Acinetobacter baumannii</i> Sample ID E796210	> 64	32	> 16	8	8	> 4	> 8	64	64	0.06	2

AMK = amikacin; AZT = aztreonam; CAZ/AVI = ceftazidime-avibactam; CEF/TAZ = ceftolozane-tazobactam; CFDC = cefiderocol; CFPM = cefepime; CPFX = ciprofloxacin; CST = colistin; ID = identification; IHMA = International Health Management Associates; ID = identification; IPM = imipenem; MEPM = meropenem; MIC = minimum inhibitory concentration; NA = not available; TGC = tigecycline

**Table 5 Chest Radiograph Results**

Visit	Lung Fields/ Airways	Heart/ Vessels	Other Structures	Comparison of Lung Fields to Screening
Screening/Baseline	Consolidation, haziness in both lungs	Normal	Normal	NA
Early Assessment	Haziness in both lungs slight improved on LLLF	Normal	Normal	Improved
End of Treatment	Haziness on RLLF probably pleural effusion	Normal	Normal	Improved
Test of Cure	Marked consolidation, haziness in both lungs	Normal	Normal	No change
Follow-up	Marked consolidation, haziness in both lungs	Normal	Normal	No change

LLL = left lower lung field; NA = not applicable; RLL = right lower lung field

**Table 6 Liver Function Tests**

Visit	AST (RR = 0 to 40)	ALT (RR = 0 to 40)	ALP (RR = 0 to 190)	GGT (RR = 0 to 60)	Total Bilirubin (RR = 0 to 1.3)
Screening/Baseline	37 U/L	17 U/L	52 U/L	13 U/L	0.43 mg/dL
Early Assessment	307 U/L	154 U/L	89 U/L	29 U/L	1.14 mg/dL
End of Treatment	20 U/L	12 U/L	47 U/L	8 U/L	0.75 mg/dL
Test of Cure	19 U/L	< 6 U/L	52 U/L	10 U/L	0.47 mg/dL
Follow-up	37 U/L	20 U/L	144 U/L	27 U/L	0.85 mg/dL

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase;  
GGT = gamma-glutamyl transferase

**Table 7 Renal Function Tests**

Visit	Blood Urea Nitrogen (RR = 0 to 20)	Serum Creatinine (RR = 0 to 1.4)	Creatinine Clearance
Screening/Baseline	94.1 mg/dL	1.50 mg/dL	31.64 mL/min
Early Assessment	61.4 mg/dL	1.28 mg/dL	37.08 mL/min
End of Treatment	41.4 mg/dL	2.19 mg/dL	21.67 mL/min
Test of Cure	39.0 mg/dL	2.20 mg/dL	21.57 mL/min
Follow-up	22.6 mg/dL	1.54 mg/dL	30.82 mL/min

**Table 8**                      **Coagulation Tests**

<b>Visit</b>	<b>Platelet Count (RR = 165 to 360)</b>	<b>aPTT (RR = 23.6 to 30.9)</b>	<b>PT-INR (RR = 0.92 to 1.13)</b>
Screening/Baseline	$431 \times 10^9/\text{L}$	41.3 sec	1.46
Early Assessment	$467 \times 10^9/\text{L}$	41.3 sec	1.50
End of Treatment	$297 \times 10^9/\text{L}$	45.0 sec	2.06
Test of Cure	$306 \times 10^9/\text{L}$	37.6 sec	1.52
Follow-up	$272 \times 10^9/\text{L}$	32.8 sec	1.30

aPTT = activated partial thromboplastin time; PT-INR = prothrombin international normalized ratio;  
RR = reference range

## Subject ID Patient # 34

Subject ID	Patient # 34	Country	Israel			
Age	78	Clinical Diagnosis at Screening	cUTI			
Gender	Female	Severity	Severe			
Race	White	APACHE II Score	27			
Height (cm)	162.0	Causative Pathogen at Screening	Pseudomonas aeruginosa			
Body Weight (kg)	68.9	CR Evidence at Screening (other than central lab)	Treatment failure CR-GNB			
MIC of Meropenem	8 µg/mL	MIC of Cefiderocol	1 µg/mL			
MIC of Imipenem	2 µg/mL					
Duration of Study Treatment	2 days	Standard of Care	Amikacin (750 mg oral)			
Study Drug	Cefiderocol (1.5 g q8h IV)					
Microbiological Results at TOC		Day 28 All-cause Mortality		Clinical Outcome at TOC		
Indeterminate		Death (Day 2)		Indeterminate		
Medical History (Ongoing)	Moderate renal failure (Day -59); ARDS (Day -43); anoxic brain damage (Day -26)					
Medical History (Not Ongoing)	Tobacco user disorder; anemia, coma hypoxic, hemorrhage of lung, mitral valve disorder, unspecified pleural effusion; acute cholecystitis, mechanical ventilation, MI, pulmonary edema (Day -58); PCI (Day -49); tracheostomy (Day -42); acute respiratory failure, pressure ulcer; cholecystostomy (Day -38); thoracentesis (Day -37)					
Adverse Event	Day	Severity	Action Taken with Study Drug	Outcome	Causality	Serious
Septic shock	2	Severe	Dose not changed	Fatal	Not related	Yes
Narrative Summary						
<p>A 78-year-old white European female from Israel had a history of tobacco use disorder, anemia, mitral valve disorder, and moderate renal failure on Day -59.</p> <p>The patient was hospitalized from home as an urgent admission onto the general ward due to an infection on Day -59. On Day -58, she had a MI and acute cholecystitis. Piperacillin/tazobactam was provided (unk until Day -5). On Day -58, she was placed on mechanical ventilation and underwent a PCI on Day -49. It was reported that the patient was in a hypoxic coma and experienced a hemorrhage of the lung. On Day -43, ARDS was reported, and the patient underwent a tracheostomy on Day -42. Acute respiratory failure was reported on an unknown date, and the patient was transferred to ICU on Day -38 (until Day -18). She underwent a cholecystostomy on Day -38, and a thoracentesis was performed on Day -37.</p> <p>On Day -8, the patient had an acute MI with ischemic cardiomyopathy, EF 45%, intubated, and subsequently had acute cholecystitis with drainage, and developed anoxic brain damage. On Day -6, the patient received chloramphenicol 500 mg q24h for 4 subsequent days until Day -2. The patient recovered minimal consciousness in the week prior to randomization and deteriorated again due to infection and was diagnosed with UTI <i>Pseudomonas</i> carbapenemase and was included in the trial.</p> <p>Urine culture samples were collected on Day -2 (indwelling catheter) showed <i>P. aeruginosa</i>, <math>\geq 1.0 \times 10^5</math> (resulted Day 1). On Day -1, cUTI was reported. Treatment included ampicillin, metronidazole and gentamicin (Days -2 to 1). The patient was screened and enrolled into the study based on treatment failure CR-GNB. Signs and symptoms included mild chills/rigor and severe vomiting. Blood sample</p>						

results showed an elevated WBC on Day 1.

On Day 1, the patient was randomized to the cefiderocol arm and received 3 doses of study drug, 1.5 g q8h. There was no evidence of drug reaction reported such as rash or angioedema. A pressure ulcer was reported on Day 2 (no staging or location was provided).

On Day 2, the patient's condition continued to deteriorate, and the SAE of septic shock (severe) was reported. Action taken with study drug was dose not changed, and the outcome of the SAE was Fatal. The investigator considered the SAE of septic shock to be not related to study drug. The patient was found dead with dilated pupils, was not resuscitated, and cause of death was reported as probably due to sepsis. The investigator could not exclude MI secondary to sepsis with the patient's background of a recent MI.

The patient did not complete study treatment (EOT), she expired on Day 2. Clinical outcome was indeterminate.

APACHE = Acute Physiology and Chronic Health Evaluation; ARDS = acute respiratory distress syndrome; CR = carbapenem resistance; cUTI = complicated urinary tract infection; EF = ejection fraction; EOT = End of Treatment; GNB = Gram-negative bacteria; ICU = intensive care unit; ID = identification; IV = intravenous; MI = myocardial infarction; MIC = minimum inhibitory concentration; NA = not available; PCI = percutaneous coronary intervention; q8h = every 8 hours; q24h = every 24 hours; SAE = serious adverse event; TOC = Test of Cure; UTI = urinary tract infection; WBC = white blood cell

**Study qualifying diagnosis:** Complicated urinary tract infection due to *P. aeruginosa* identified to be carbapenem resistant through treatment failure of CR-GNB.

**Study qualifying infection history:** Two days prior to study entry, *P. aeruginosa* was identified from a urine specimen and was resistant to aztreonam, cefepime, ceftazidime-avibactam, and ciprofloxacin. The isolate was susceptible to ceftolozane-tazobactam, colistin, and imipenem, and intermediate sensitivity was noted for meropenem and amikacin (Table 3).

**Current hospitalization history:** The patient was hospitalized from home as an urgent admission onto the general ward due to an infection on Day -59. She had an MI on Day -58. She was on continuous mandatory ventilation (CMV) from Day -58 to Day 2.

On Day -58, she developed pulmonary edema and acute cholecystitis. Several days later, she underwent a PCI on Day -49. On Day -42, the patient had a tracheostomy and remained attached to CMV. She also experienced hemorrhage of the lung. On Day -39, fluconazole 400 mg q24h was administered for pressure ulcer.

The patient was transferred into the ICU on Day -38 due to acute respiratory failure and pulmonary edema with acute respiratory distress syndrome. A few weeks later, on Day -18, the patient was transferred to the Department of Internal Medicine. On Day -8, the patient had an acute MI with ischemic cardiomyopathy EF 45%, and later developed acute cholecystitis with drainage. It was reported that on Day -8, paracetamol was administered for unspecified pleural effusion, and the patient received 2 units of blood for anemia on the same day and then 1 unit 1 week later. She had a cholecystectomy on Day -38 and a thoracentesis on Day -37. On Day -6, the patient received chloramphenicol 500 mg q24h for 4 subsequent days until Day -2. It was reported that she had some recovery with minimal consciousness, but in the week before randomization deteriorated again due to infection, confirmed with elevated inflammatory markers. She was

diagnosed with UTI-carbapenemase-producing *Pseudomonas* carbapenemase (from a urine sample on Day -32, showing *P. aeruginosa*) and was, therefore, eligible for the study. A chest radiograph was completed (date not specified) and showed more infiltrates, but could not confirm ventilator-associated pneumonia. She was placed into isolation on Day 1.

The patient was treated with ampicillin 1 g IV q24h, metronidazole 500 mg and gentamicin 240 mg IV q24h from Day -2 to Day 1.

**Clinical course:** On Day -2 (Screening/Baseline), a microbiological laboratory sample was obtained from the urine (indwelling catheter). The pathogen *P. aeruginosa* (quantitation,  $\geq 1.0 \times 10^5$ ) was identified.

On Day 1, the patient was on a CMV from Day -58 to Day 1. Arterial blood gases showed PaO<sub>2</sub> at 91 mm Hg, PaCO<sub>2</sub> at 50 mm Hg, SaO<sub>2</sub> at 95%, and FiO<sub>2</sub> at 21%. An initial clinical assessment of signs and symptoms was performed and mild chills/rigor and severe vomiting were noted. The Sequential Organ Failure Assessment (SOFA) score was 7, and the Clinical Pulmonary Infection Score (CPIS) was 2 (Table 2). The inflammatory indices of WBC count, C-reactive protein (CRP), and body temperature were  $26.10 \times 10^9/L$ , 276.8 mg/L, and 37.9°C, respectively (Table 1).

Blood urea nitrogen and creatinine were 72.8 mg/dL and 1.3 mg/dL, respectively. Alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma glutamyl transferase, and total bilirubin were 23 U/L, 29 U/L, 324 U/L, 313 U/L, and 0.7 mg/dL, respectively. Hemoglobin was 8.71 g/dL. No electrocardiogram was performed at Screening/Baseline.

The patient received the first infusion of cefiderocol 1.5 g q8h IV on Day 1. She received 2 subsequent infusions on Day 1 and Day 2.

The patient experienced the SAE of septic shock on Day 2. The patient died due to the SAE. The investigator considered the SAE not related to study drug. The patient was found dead with dilated pupils, not resuscitated, and cause of death was probably due to sepsis. The investigator could not exclude MI secondary to sepsis with the patient's background of a recent MI. The clinical outcome was indeterminate.

**Table 1 Inflammatory Indices**

Visit	White Blood Cell Count (RR = 4 to 11)	C-reactive Protein (RR = 0 to 6)	Body Temperature
Screening/Baseline	$26.10 \times 10^9/L$	276.8 mg/L	37.9°C

RR = reference range

**Table 2 Sequential Organ Failure Assessment and Total Clinical Pulmonary Infection Score Status**

Visit	SOFA Score	Total CPIS
Screening/Baseline	7	2

CPIS = Clinical Pulmonary Infection Score; SOFA = Sequential Organ Failure Assessment

**Table 3 Antimicrobial Susceptibility Testing at Screening (European Committee on Antimicrobial Susceptibility Testing)**

Pathogen	Resistant	Intermediate	Susceptible	Not Applicable
<i>Pseudomonas aeruginosa</i>	Aztreonam, cefepime, ceftazidime-avibactam, ciprofloxacin	Meropenem, amikacin	Ceftolozane-tazobactam, colistin, imipenem	Cefiderocol, tigecycline

**Table 4 Susceptibility Testing at Each Visit**

Visit	IHMA Organism ID	AMK	AZT	CFPM	CAZ/AVI	CEF/TAZ	CPFX	CST	IPM	MEPM	CFDC	TGC
		MIC µg/mL										
Screening/ Baseline	<i>Pseudomonas aeruginosa</i> Sample ID E629381	16	> 32	> 16	32	4	4	2	2	8	1	> 4

AMK = amikacin; AZT = aztreonam; CAZ/AVI = ceftazidime-avibactam; CEF/TAZ = ceftolozane-tazobactam; CFDC = cefiderocol; CFPM = cefepime; CPFX = ciprofloxacin; CST = colistin; ID = identification; IHMA = International Health Management Associates; IPM = imipenem; MEPM = meropenem; MIC = minimum inhibitory concentration; TGC = tigecycline

**Table 5 Liver Function Tests**

Visit	AST (RR = 6 to 32)	ALT (RR = 6 to 31)	ALP (RR = 35 to 104)	GGT (RR = 7 to 36)	Total Bilirubin (RR = 0.2 to 1.2)
Screening/Baseline	29 U/L	23 U/L	324 U/L	313 U/L	0.7 mg/dL

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase;  
GGT = gamma-glutamyl transferase; RR = reference range

**Table 6 Renal Function Tests**

Visit	Blood Urea Nitrogen (RR = 15 to 40)	Serum Creatinine (RR = 0.6 to 1.1)	Creatinine Clearance
Screening/Baseline	72.8 mg/dL	1.3 mg/dL	37.9 mL/min

RR = reference range

**Table 7 Coagulation Tests**

Visit	Platelet Count (RR = 150 to 400)	aPTT (RR = 24 to 34)	PT-INR (RR = 0.85 to 1.2)
Screening/Baseline	$221 \times 10^9/L$	25.3 sec	1.55

aPTT = activated partial thromboplastin time; PT-INR = prothrombin international normalized ratio;  
RR = reference range

## Subject ID Patient # 39

Subject ID	Patient # 39	Country	Greece			
Age	73	Clinical Diagnosis at Screening	BSI			
Gender	Female	Severity	Severe			
Race	White	APACHE II Score	22			
Height (cm)	158.0	Causative Pathogen at Screening	Klebsiella pneumoniae			
Body Weight (kg)	73.0	CR Evidence at Screening (other than central lab)	Treatment failure CR-GNB			
MIC of Meropenem	> 64 µg/mL	MIC of Cefiderocol	8 µg/mL			
MIC of Imipenem	> 64 µg/mL					
Duration of Study Treatment	10 days	Standard of Care	Colistin (12 million IU IV), Fosfomycin (24 g IV)			
Study Drug Treatment	Fosfomycin (4 g q4h, 6 g q6h, 6g q12h; IV); colistin (6 million U q12h, 3 million U q24h; IV); meropenem (2 g q8h IV)					
Microbiological Results at TOC		Day 28 All-cause Mortality		Clinical Outcome at TOC		
Microbiological persistence		Death (Day 17)		Clinical failure (EOT)		
Medical History (Ongoing)	Parkinson's disease, impaired level of consciousness, acute kidney injury, ischemic acute liver failure, hypoalbuminemia, fever, anemia, hypotension, septic shock, respiratory failure, suspected candidiasis, suspected Clostridium difficile colitis, thrombopenia; septic encephalopathy					
Medical History (Not Ongoing)	Arterial hypertension; ileus					
Adverse Event	Day	Severity	Action Taken with Study Drug	Outcome	Causality	Serious
Refractory septic shock	16	Severe	Not applicable	Fatal	Not related	Yes
Narrative Summary						
<p>A 73-year-old white female from Greece had a medical history of Parkinson's disease and was admitted from home to the hospital on Day -20 due to the disease. It was reported that the patient had impaired level of consciousness, acute kidney injury, and ischemic acute liver failure. On the same day (Day -20), she experienced respiratory failure, was intubated, placed on mechanical ventilation, and transferred to ICU. On Day -17, mechanical ventilation stopped. The patient developed a fever on Day -13 and blood cultures obtained isolated <i>K. pneumoniae</i>. Daptomycin (Days -13 to -12), cefepime (Days -13 to -7), and colistin (Days -10 to 1) were administered.</p> <p>On Day -9, the patient's general condition deteriorated with ileus, hypotension, septic shock, and respiratory failure. She was re-intubated and placed on mechanical ventilation on the same day (Day -9). It was reported that a repeat blood culture detected <i>K. pneumoniae</i>. Fosfomycin (Days -8 to 1) and tigecycline (Days -5 to -3) were administered. Candidiasis was suspected on Day -8 and was treated with micafungin (Days -8 to 13). The following day, on Day -7, <i>C. difficile</i> colitis was also suspected and treated with vancomycin (Days -7 to 4). Treatment for ileus included erythromycin (Days -5 to -1). On Day -4, the patient had thrombocytopenia.</p> <p>On Day 1, the patient was diagnosed with BSI (onset date of infection was Day -13). She was screened and randomized to the BAT group on the same day (Day 1). SOFA score was 16 and blood culture obtained (on Day -2) isolated <i>K. pneumoniae</i>. Fosfomycin (Days 1 to 9) and colistin (Days 2 to 9) were administered.</p> <p>On Day 4, EA, the SOFA score was 17 and blood cultures were negative. The clinical outcome was</p>						

assessed as a clinical failure with microbiological eradication. Meropenem (Days 8 to 9) was administered.

On Day 10, EOT, the SOFA score was 18 and blood cultures were negative. Clinical outcome was assessed as clinical failure and microbiological outcome was assessed as indeterminate. Meropenem, fosfomycin, and colistin were administered (Days 10 to 17).

It was reported that organ failures (respiratory, renal, and hepatic) persisted and on Day 16, the patient's condition further deteriorated with refractory septic shock. On Day 17, the patient expired.

APACHE = Acute Physiology and Chronic Health Evaluation; ARDS = acute respiratory distress syndrome; BAL = bronchoalveolar lavage; BAT = best available therapy; BSI = blood stream infection; CR = carbapenem resistance; EA = Early Assessment; EOT = End of Treatment; ID = identification; IV = intravenous; MIC = minimum inhibitory concentration; q4h = every 4 hours; q6h = every 6 hours; q8h = every 8 hours; q12h = every 12 hours; q24h = every 24 hours; SAE = serious adverse event; SOFA = Sequential Organ Failure Assessment; TOC = Test of Cure; unk = unknown

**Study Qualifying Diagnosis:** Blood stream infection due to *K. pneumoniae* was identified with evidence of carbapenem resistance through treatment failure (CR-GNB).

**Study Qualifying Infection History:** At the Screening/Baseline visit, a blood sample showed *K. pneumoniae* resistant to amikacin, aztreonam, cefepime, ceftazidime-avibactam, ceftolozane-tazobactam, ciprofloxacin, imipenem, and meropenem. The isolate was susceptible to colistin and tigecycline (Table 3).

**Current Hospitalization History:** On Day -20, the patient was admitted to the general ward from home as an elective admission due to Parkinson's disease and had impaired level of consciousness, acute kidney injury, and ischemic acute liver failure. The patient was receiving ventilation beginning on Day -19. The patient developed a fever, and her general condition deteriorated with ileus and hypotension, and she was diagnosed with septic shock. The onset date of the infection was Day -13.

Daptomycin was given from Day -13 to Day -12. Intravenous colistin was administered on Day -10 to Day 1. Cefepime was administered from Day -13 to Day -7. Tigecycline was administered from Day -5 to Day -3. Oral erythromycin was administered from Day -5 to Day -1 for ileus.

**Clinical Course:** On Day -2, a microbiological laboratory specimen was obtained from the blood. The pathogen *K. pneumoniae* (no quantitation) was identified.

On Day 1 (Screening/Baseline), a blood culture sample was negative. Arterial blood gases (ABGs) showed PaO<sub>2</sub> 94 mm, PaCO<sub>2</sub> 31 mm, SaO<sub>2</sub> 98%, and FiO<sub>2</sub> 36%. Signs and symptoms at the clinical assessment showed severe signs and symptoms of the causative infection. The SOFA score was 16 (Table 2). The inflammatory indices of white blood cell (WBC) count, C-reactive protein (CRP), and body temperature were  $9.9 \times 10^9/L$ , 6.9 mg/dL, and 35.8°C, respectively (Table 1).

Treatment with the BAT was initiated on Day 1 and consisted of fosfomycin 4 g IV q4h for 23 doses from Day 1 to Day 5, then adjusted for renal function to 6 g q6h for 12 doses from Day 5 to Day 9, and 6 g q12h for 1 dose on Day 9 and colistin 6 million U IV q12h for 2 doses on Day 2, then 3 million U IV q24h for 5 doses from Day 3 to Day 7, and

6 million U IV q12h for 4 doses from Day 8 to Day 9. Meropenem 2 g IV was administered on Day 8 to Day 9.

On Day 4 (EA), 2 microbiological laboratory samples were obtained from the blood and the results were negative. The arterial blood gases showed PaO<sub>2</sub> 89 mm Hg, PaCO<sub>2</sub> 30 mm Hg, SaO<sub>2</sub> 98%, and FiO<sub>2</sub> 40%. No new signs or symptoms were noted. The SOFA score was 17; worsened from the Screening/Baseline visit. The inflammatory indices of WBC count, CRP, and body temperature were  $12.7 \times 10^9/\text{L}$ , 6.9 mg/dL, and 38.8°C, respectively. The patient was considered a clinical failure with microbiological eradication.

On Day 6, a microbiological laboratory specimen was obtained from the blood. The pathogen *Providencia stuartii* (no quantitation) was identified.

On Day 10 (EOT), 2 microbiological laboratory samples were taken from the blood and the results were negative. The patient completed treatment with BAT. The ABG analysis showed PaO<sub>2</sub> 89 mm Hg, PaCO<sub>2</sub> 25 mm Hg, SaO<sub>2</sub> 98%, and FiO<sub>2</sub> 40%. No new signs or symptoms were noted. The SOFA score was 18; worsened from the Screening/Baseline visit. The inflammatory indices of WBC count, CRP, and body temperature were  $8 \times 10^9/\text{L}$ , 10.7 mg/dL, and 38.0°C, respectively. The clinical outcome was assessed as a clinical failure with an indeterminate microbiological outcome. Meropenem and colistin were started for the treatment of the target disease.

At unscheduled visits on Day 13 and Day 15 (TOC), microbiological laboratory specimens were obtained from the blood. The pathogen *K. pneumoniae* (no quantitation) was identified. The patient was considered a clinical failure with microbiological persistence.

On Day 16, there was further deterioration, and the septic shock became refractory.

On Day 17, the patient expired due to severe refractory septic shock. The investigator considered the event serious and not related to the study drug or to the study conduct.

**Table 1 Inflammatory Indices**

Visit	White Blood Cell Count (RR = 4.5 to 10)	C-reactive Protein (RR = 0 to 0.7)	Body Temperature
Screening/Baseline	$9.9 \times 10^9/\text{L}$	6.9 mg/dL	35.8°C
Early Assessment	$12.7 \times 10^9/\text{L}$	6.9 mg/dL	38.8°C
End of Treatment	$8 \times 10^9/\text{L}$	10.7 mg/dL	38.0°C

RR = reference range

**Table 2 Sequential Organ Failure Assessment Status**

Visit	SOFA Score
Screening/Baseline	16
Early Assessment	17
End of Treatment	18

SOFA = Sequential Organ Failure Assessment

**Table 3 Antimicrobial Susceptibility Testing at Screening  
(European Committee on Antimicrobial Susceptibility Testing)**

Pathogen	Resistant	Intermediate	Susceptible	Not Applicable
<i>Klebsiella pneumonia</i>	Amikacin, aztreonam, cefepime, ceftazidime-avibactam, ceftolozane-tazobactam, ciprofloxacin, imipenem, meropenem	NA	Colistin, tigecycline	Cefiderocol

NA = not applicable

**Table 4 Susceptibility Testing at Each Visit**

Visit	IHMA Organism ID	AMK	AZT	CFPM	CAZ/ AVI	CEF/ TAZ	CPFX	CST	IPM	MEPM	CFDC	TGC
		MIC µg/mL										
Screening/ Baseline	<i>Klebsiella pneumoniae</i> Sample ID E406713	> 64	> 32	> 16	> 64	> 64	> 4	≤ 0.5	> 64	> 64	8	0.5
Day 13, Unscheduled 1 (Day 13)	<i>Klebsiella pneumoniae</i> Sample ID EL406698	> 64	> 32	> 16	> 64	> 64	> 4	> 8	64	> 64	16	0.5
Day 15, Unscheduled 2 (Day 15)	<i>Klebsiella pneumoniae</i> Sample ID E406697	> 64	> 32	> 16	> 64	> 64	> 4	> 8	64	> 64	4	0.5

AMK = amikacin; AZT = aztreonam; CAZ/AVI = ceftazidime-avibactam; CEF/TAZ = ceftolozane-tazobactam; CFDC = cefiderocol; CFPM = cefepime; CPFX = ciprofloxacin; CST = colistin; IHMA = International Health Management Associates; IPM = imipenem; MEPM = meropenem; MIC = minimum inhibitory concentration; TGC = tigecycline

**Table 5 Liver Function Tests**

Visit	AST (RR = 0 to 31)	ALT (RR = 0 to 34)	ALP (RR = 0 to 120)	GGT (RR = 0 to 38)	Total Bilirubin (RR = 0 to 1.1)
Screening/Baseline	108 IU/L	34 IU/L	133 IU/L	341 U/L	10.10 mg/dL
Early Assessment	103 IU/L	34 IU/L	88 IU/L	539 U/L	14.83 mg/dL
End of Treatment	215 IU/L	61 IU/L	193 IU/L	633 U/L	12.53 mg/dL

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase;  
GGT = gamma-glutamyl transferase; RR= reference range

**Table 6 Renal Function Tests**

Visit	Blood Urea Nitrogen (RR = 0 to 43)	Serum Creatinine (RR = 0 to 1.25)	Creatinine Clearance
Screening/Baseline	17.29 mg/dL	1.31 mg/dL	44.077 mL/min
Early Assessment	33.64 mg/dL	2.44 mg/dL	23.66 mL/min
End of Treatment	34.07 mg/dL	2.31 mg/dL	25.00 mL/min

NA = not available; RR = reference range

**Table 7 Coagulation Tests**

Visit	Platelet Count (RR = 140 to 440)	aPTT (RR = 25 to 35)	PT-INR (RR = 0.85 to 1.15)
Screening/Baseline	$37 \times 10^9/L$	39.7 sec	2.51
Early Assessment	$53 \times 10^9/L$	32.6 sec	2.78
End of Treatment	$20 \times 10^9/L$	34 sec	2.59

aPTT = activated partial thromboplastin time; PT-INR = prothrombin international normalized ratio; RR = reference range

## Subject ID Patient # 40

Subject ID		Patient # 40		Country		Turkey	
Age		84		Clinical Diagnosis at Screening		VAP	
Gender		Female		Severity		Severe	
Race		White		APACHE II Score		22	
Height (cm)		165.0		Causative Pathogen at Screening		Klebsiella pneumoniae	
Body Weight (kg)		82.0		CR Evidence at Screening (other than central lab)		Positive rapid diagnostic test (Xpert Carba-R)	
MIC of Meropenem		> 64 µg/mL		MIC of Cefiderocol		4 µg/mL	
MIC of Imipenem		> 64 µg/mL					
Duration of Study Treatment		12 days		Standard of Care		Tigecycline (150 mg IV), Colistin (50 mg IV)	
Study Drug		BAT (tigecycline 50 mg q24h IV; colistin 150 mg q24h IV; meropenem 1g q24h IV)					
Microbiological Results at TOC				Day 28 All-cause Mortality		Clinical Outcome at TOC	
Persistence				Death (Day 24)		Clinical failure	
Medical History (Ongoing)		Diabetes mellitus, hypertension, chronic disease anemia, chronic obstructive pulmonary disease, chronic ischemic heart disease, CHF, chronic renal failure, acute respiratory failure, necrotic scar on the left foot, grade 1 decubitus ulcer in the sacral and right scapular region, anuria, hypoalbuminemia, sepsis					
Medical History (Not Ongoing)		Pneumonia; urinary tract infection, public-acquired pneumonia					
Adverse Event	Day	Severity	Action Taken with Study Drug	Outcome	Causality	Serious	
Increase of INR	3	Mild	Dose not changed	Recovered/resolved	Not related	No	
Elevated LFTs	4	Severe	Dose not changed	Recovered/resolved	Not related	Yes	
Invasive candidiasis	4	Mild	Dose not changed	Recovered/resolved	Not related	No	
Worsening of sepsis	4	Moderate	Dose increased	Recovered/resolved	Related	No	
Cardiac arrest	11	Severe	Dose not changed	Recovered/resolved	Not related	Yes	
Decrease of platelet	13	Mild	NA	Recovered/resolved	Not related	No	
Worsening of chronic disease anemia (low hemoglobin)	13	Mild	NA	Recovered/resolved	Not related	No	

Worsening of chronic disease anemia (low hemoglobin)	21	Mild	NA	Recovered/resolved	Not related	No
Hypokalemia	22	Mild	NA	Recovered/resolved	Not related	No
Septic shock	23	Severe	NA	Not recovered/not resolved	Related	Yes
Cardiac arrest (time: 02:05)	24	Severe	NA	Recovered/resolved	Not related	Yes
Cardiac arrest (time: 10:40)	24	Severe	NA	Fatal	Not related	Yes

#### Narrative Summary

An 84-year-old white female from Turkey had a medical history of diabetes mellitus, hypertension, chronic disease anemia, COPD, chronic ischemic heart disease, CHF, chronic renal failure, and pneumonia (with hospitalization). The investigator reported that the patient had chronic renal failure and was on a hemodialysis program every 2 days.

The patient was hospitalized from home on Day -12 with acute respiratory failure and pneumonia. She was transferred to the current hospital ICU on Day -2. A grade 1 decubitus ulcer in the sacral and right scapular region (measurements not given) was reported with a necrotic scar of the left foot (Day -12). On the previous hospital ICU admission, *Enterococcus sp.* was isolated from the urine culture and *Klebsiella sp.* was isolated from the TA; vancomycin-resistant *Enterococcus* was isolated from the rectal swab culture. On Day -12, ampicillin sulbactam and clarithromycin were both provided until Day -6. On Day -12, the patient was attached to a mechanical ventilator and anuria was reported. Moxifloxacin was provided for the (public acquired) pneumonia on Day -6 to Day -2. Vancomycin was provided on Day -2 with tigecycline and colistin provided from Day -1 to Day 1. On Day 1, the patient was enrolled in the study with the diagnosis of VAP. Chest x-ray showed patchy consolidation of the right lower zone. Rapid diagnosis was positive for NDM and OXA48 genes, on this date, from a lung specimen culture utilizing Xpert Carba-R. TA and blood cultures were collected on Day -2 and both were positive for *K. pneumoniae* (results Day 1).

On Day 1, the patient was randomized to the BAT arm. Colistin (150 mg BID) and tigecycline (50 mg BID) were provided (until Day 12). Meropenem 1 g q24h was added on Day 3 (until Day 12) due to treatment failure (reason for change). On Day 3, TA cultures grew CR *K. pneumoniae*. The patient was on amiodarone from Day 1 to Day 2.

On Day 4, EA, chest x-ray showed no change of lung fields in comparison to Screening. Blood sample results showed a high WBC count ( $30.24 \times 10^9/L$ ) with raised neutrophils. The patient had experienced the unrelated severe SAE of elevated LFTs (up to 8 times above normal RR): ALT 322.7 U/L (RR  $\leq 33$ ), AST 364.7 U/L (RR  $\leq 32$ ), and PT-INR 3.69 (RR 0.8 to 1.2). The investigator reported the LFTs elevations were due to sepsis and clinical failure. TA culture was positive and *K. pneumoniae* and *Morganella morganii* were identified (Day 5). Clinical outcome was assessed as clinical failure. On the same day, Day 4, the mild unrelated AE of invasive candidiasis was reported. Micafungin was provided until Day 12. The investigator reported the AE outcome to be recovered/resolved on Day 13.

On Day 4, the AE of worsening of sepsis was reported. The outcome of the AE was reported as recovered/resolved on Day 10, and the causality was reported to be related to inefficacy of BAT.

On Day 11, the SAE of cardiac arrest (first) was reported. The investigator reported that the patient was successfully resuscitated for 10 minutes and survived. Prior to the cardiac arrest, she had been extubated, and post CPR she was reintubated and her ICU stay was extended. The SAE causality was reported as not related to study drug.

On Day 12, EOT, chest x-ray showed no change compared to baseline. The TA culture (collected Day 13) isolated *K. pneumoniae* (resulted on Day 16). Clinical and microbiological outcomes were

assessed as clinical failure and persistence, respectively. No antibiotic was given after the failure between Day 12 and Day 23. On Day 13, the mild unrelated AE of decrease of platelet was reported. The outcome of the event was recovered/resolved on Day 15. Fresh frozen plasma was provided (Day 18 to Day 22).

On Day 19, TOC, chest x-ray showed no change in comparison to Screening. TA cultures remained positive for CR *Klebsiella* and *P. aeruginosa*. Clinical and microbiological outcomes were assessed as clinical failure and persistence, respectively. On Day 21, the mild unrelated AE of worsening of chronic disease anemia (low hemoglobin) was reported and resolved the next day (Day 22).

The patient developed the SAE of septic shock on Day 23 (25th day of ICU stay). Antibiotics including colistin, tigecycline, and meropenem were initiated. The causality of the SAE was reported as related to inefficacy of BAT.

On Day 24, the SAE of cardiac arrest (second event) occurred while the patient was on inotropics. CPR was initiated, and she was successfully resuscitated after 4 minutes of CPR. On the same day, the SAE of cardiac arrest (third event) occurred. Despite 30 minutes of resuscitation and sequential adrenaline injections, the patient expired. The investigator reported that the patient died due to cardiopulmonary arrest that occurred during sepsis and the causality of the SAE was not related to study drug.

AE= adverse event; APACHE = Acute Physiology and Chronic Health Evaluation; ALT = alanine transaminase; AST = aspartate transaminase; BAT = best available therapy; BID = twice daily; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; CPR = cardiopulmonary resuscitation; CR = carbapenem resistant; EA = Early Assessment; EOT = End of Treatment; ICU = intensive care unit; ID = identification; IV = intravenous; LFTs = liver function tests; MIC = minimum inhibitory concentration; NA = not available; PT-INR = prothrombin international normalized ratio; q24h = every 24 hours; RR = reference range; SAE = serious adverse event; TA = tracheal aspirate; TOC = Test of Cure; unk = unknown; VAP = ventilator-associated pneumonia; WBC = white blood cell

**Study qualifying diagnosis:** Ventilator-associated pneumonia due to *K. pneumoniae* with evidence of CR through a positive rapid diagnostic test (Xpert Carba-R [NDM and OXA48])

**Study qualifying infection history:** On Day 1, a sample obtained from the TA showed *K. pneumoniae* resistant to amikacin, aztreonam, cefepime, ceftazidime-avibactam, ceftolozane-tazobactam, ciprofloxacin, imipenem, meropenem (Table 3). The isolate was susceptible to colistin and tigecycline.

**Current hospitalization history:** The patient was hospitalized on Day -2 as an urgent admission onto the ICU due to the current infection of VAP. The patient was transferred from another hospital, where she had been confined in the ICU since Day -12. The onset date of infection was Day -2. The patient was placed on synchronized intermittent mandatory ventilation (SIMV) on Day -12 through Day 24.

**Clinical course:** On Day -2, a microbiological laboratory sample was obtained from the TA and WBC polymorphs (3+,  $\geq 25$ , many) were noted. Gram-negative rods (+) were identified. The pathogen *K. pneumoniae* was identified. An additional microbiological laboratory sample was obtained from the blood for examination. Gram-negative rods (+) were identified. The pathogen *K. pneumoniae* was identified. On repeat tests of TA and blood cultures on Day 1 (at time of randomization as per protocol), only the TA was positive for Gram-negative rods and *K. pneumoniae*. WBC polymorphs (3+,  $\geq 25$ , many) were noted.

On Day -1, the chest radiograph showed patchy consolidation area of right lower zone (Table 5).

On Day 1 (Screening/Baseline), rapid diagnosis was positive for NDM and OXA48 genes, from a lung specimen culture utilizing Xpert Carba-R (NDM and OXA48).

A microbiological laboratory specimen was obtained from the TA, and WBC polymorphs (3+,  $\geq 25$ , many) were noted. Gram-negative rods (+) were identified. The pathogen *K. pneumoniae* was identified. A microbiological laboratory specimen was obtained from the blood. Culture results were negative. The patient was on mechanical ventilation since Day -12 and was receiving supplemental oxygen; pulse oximetry indicated SpO<sub>2</sub> 100% (FiO<sub>2</sub> 40%). The initial clinical assessment of signs and symptoms revealed moderate malaise, expectorated sputum production, wheezing, rales, dullness on percussion, and bronchial breath sounds; and severe fatigue, dyspnea (including retractions), and suctioned respiratory secretions. The Sequential Organ Failure Assessment (SOFA) score was 9, and the Clinical Pulmonary Infection Score (CPIS) was 5 (Table 2). The inflammatory indices of WBC count, C-reactive protein (CRP), and body temperature were  $35.29 \times 10^9/\text{L}$ , 78.77 mg/dL, and 37.1°C, respectively (Table 1).

The patient received her first dose of BAT consisting of tigecycline (50 mg, q24h IV) on Day 1 and received 11 subsequent doses of tigecycline on Day 2 through Day 12. The patient received colistin (150 mg, q24h, IV) on Day 1 and received 9 subsequent doses on Day 2 through Day 12. The patient received meropenem 1 g q24h IV on Day 4 through Day 12.

On Day 3, the chest radiograph showed patchy consolidation area of right lower zone and no change compared to lung fields at Screening.

On Day 4 (EA), a microbiological laboratory sample was obtained from the TA, and WBC polymorphs (3+,  $\geq 25$ , many) were noted. Gram-negative rods (2+) were identified. The pathogens *K. pneumoniae* and *Morganella morganii* were identified. The patient was receiving supplemental oxygen via a ventilator; pulse oximetry indicated SpO<sub>2</sub> 100%, and FiO<sub>2</sub> 40%. Signs and symptoms revealed moderate expectorated sputum production, dullness on percussion, and bronchial breath sounds; and severe fatigue, malaise, dyspnea (including retractions), suctioned respiratory secretions, and rales. The SOFA score was 11, and the CPIS was 5. The inflammatory indices of WBC count, CRP, and body temperature were  $30.24 \times 10^9/\text{L}$ , 185.95 mg/dL, and 37.1°C, respectively. The patient had experienced the SAE of elevated LFTs (up to 8 times above normal RR): ALT 322.7 U/L (RR  $\leq 33$  U/L), AST 364.7 U/L (RR  $\leq 32$  U/L), and PT-INR 3.69 (RR 0.8 to 1.2). The dose of study drug was not changed and the patient recovered from the event on Day 13. The investigator considered the elevated LFTs to be due to sepsis and not related to study drug. The patient was considered a clinical failure.

On Day 11, the patient experienced the SAE of cardiac arrest (first event). Treatment included epinephrine. The patient recovered from the event. The investigator considered the event severe and not related to study drug.

On Day 12 (EOT), the chest radiograph showed patchy consolidation area of right lower zone persisting and no change compared to lung fields at Screening. The patient was receiving supplemental oxygen; pulse oximetry showed an SpO<sub>2</sub> of 100% and FiO<sub>2</sub> 60%. The clinical signs and symptoms included moderate fatigue, malaise, and dyspnea (including retractions), suctioned respiratory secretions, rales, and expectorated sputum production. The SOFA score was 12 and the CPIS was 3. The inflammatory indices of WBC count, CRP, and body temperature were  $10.06 \times 10^9/L$ , 75.84 mg/dL, and 36.6°C, respectively. The patient was considered a clinical failure with microbiological persistence. No antibiotic was given between Day 12 and Day 23.

On Day 13, a microbiological laboratory sample was obtained from the TA and WBC polymorphs (3+,  $\geq 25$ , many) and squamous epithelial cells (1+,  $< 10$ , few) were noted. Gram-negative rods (+) were identified. The pathogen *K. pneumoniae* was identified.

On Day 19 (TOC), a microbiological laboratory sample was obtained from the TA, and WBC polymorphs (3+,  $\geq 25$ , many) were noted. Gram-negative rods (2+) were identified. The pathogens *K. pneumoniae* and *Pseudomonas aeruginosa* were identified. The chest radiograph showed consolidation in the right lower zone positive and no change compared to lung fields at Screening. The patient was receiving supplemental oxygen; pulse oximetry showed an SpO<sub>2</sub> of 100% with FiO<sub>2</sub> 40%. Clinical signs and symptoms included moderate fatigue, malaise, dyspnea (including retractions), rales, and expectorated sputum production; and mild suctioned respiratory secretions. The SOFA score was 8 and the CPIS was 2. The inflammatory indices of WBC count, CRP, and body temperature were  $8.09 \times 10^9/L$ , 74.35 mg/dL, and 36.7°C, respectively. The patient was considered a clinical failure with microbiological persistence. The patient had a fast heart rate (132 to 152 beats per minute) and was afebrile. Blood test results showed raised partial thromboplastin time (PTT), alkaline phosphatase (ALP), AST, lactate dehydrogenase (LDH), and CRP. The patient was considered a clinical failure with microbiological persistence.

On Day 23, the patient experienced the SAE of septic shock. The patient did not recover from the event. The investigator considered the event severe and related to study drug. The patient developed hypotension (75/45 mm Hg on Day 24). The investigator explained that the clinical picture was sepsis and, therefore, wide spectrum antibiotics including colistin, tigecycline, and meropenem were initiated. Treatment also included hydrocortisone and sodium bicarbonate.

On Day 24 at 02:05 hours, the SAE of severe cardiac arrest (second) developed while the patient was on inotropics. CPR was initiated, and she was successfully resuscitated after 4 minutes of CPR. The investigator reported that causality was not related to study drug.

On the same day (Day 24) at 10:40 hours, the SAE of severe cardiac arrest (third event) developed. Despite 30 minutes of resuscitation and sequential adrenaline injections, the patient expired at 11:10 hours. The investigator reported that the patient died due to cardiopulmonary arrest that developed during sepsis, and the causality of the SAE was not related to study drug.

**Table 1 Inflammatory Indices**

Visit	White Blood Cell Count (RR = 4.4 to 11.3)	C-reactive Protein (RR = 0 to 5)	Body Temperature
Screening/Baseline	$35.29 \times 10^9/L$	78.77 mg/dL	37.1°C
Early Assessment	$30.24 \times 10^9/L$	185.95 mg/dL	37.1°C
End of Treatment	$10.06 \times 10^9/L$	75.84 mg/dL	36.6°C
Test of Cure	$8.09 \times 10^9/L$	74.35 mg/dL	36.7°C

RR = reference range

**Table 2 Sequential Organ Failure Assessment and Total Clinical Pulmonary Infection Score Status**

Visit	SOFA Score	Total CPIS
Screening/Baseline	9	5
Early Assessment	11	5
End of Treatment	12	3
Test of Cure	8	2

CPIS = Clinical Pulmonary Infection Score; SOFA = Sequential Organ Failure Assessment

**Table 3 Antimicrobial Susceptibility Testing at Screening (European Committee on Antimicrobial Susceptibility Testing)**

Pathogen	Resistant	Intermediate	Susceptible	Not Applicable
<i>Klebsiella pneumoniae</i>	Amikacin, aztreonam, cefepime, ceftazidime-avibactam, ceftolozane-tazobactam, ciprofloxacin, imipenem, meropenem	NA	Colistin, tigecycline	Cefiderocol

NA = not applicable

**Table 4 Susceptibility Testing at Each Visit**

Visit	IHMA Organism ID	AMK	AZT	CFPM	CAZ/ AVI	CEF/ TAZ	CPFX	CST	IPM	MEPM	CFDC	TGC
		MIC µg/mL										
Screening/ Baseline	<i>Klebsiella pneumoniae</i> Sample ID E873723	> 64	> 32	> 16	> 64	> 64	> 4	≤ 0.5	> 64	> 64	4	1
Early Assessment	<i>Klebsiella pneumoniae</i> Sample ID E873719	> 64	> 32	> 16	> 64	> 64	> 4	1	> 64	> 64	4	2
End of Treatment	<i>Klebsiella pneumoniae</i> Sample ID E873737	> 64	> 32	> 16	> 64	> 64	> 4	8	> 64	> 64	4	> 4
Test of Cure	<i>Klebsiella pneumoniae</i> Sample ID E873740	> 64	> 32	> 16	> 64	> 64	> 4	4	64	> 64	4	0.5

AMK = amikacin; AZT = aztreonam; CAZ/AVI = ceftazidime-avibactam; CEF/TAZ = ceftolozane-tazobactam; CFDC = cefiderocol; CFPM = cefepime; CPFX = ciprofloxacin; CST = colistin; ID = identification; IHMA = International Health Management Associates; IPM = imipenem; MEPM = meropenem; MIC = minimum inhibitory concentration; TGC = tigecycline

**Table 5 Chest Radiograph Results**

Visit	Lung Fields/ Airways	Heart/ Vessels	Other Structures	Comparison of Lung Fields to Screening
Screening/Baseline	Patchy consolidation area of right lower zone	Normal	Normal	NA
Early Assessment	Patchy consolidation area of right lower zone	Normal	Normal	No change
End of Treatment	Patchy consolidation area of right lower zone persisting	Normal	Normal	No change
Test of Cure	Consolidation in right lower zone positive	Normal	Normal	No change

NA = not applicable

**Table 6 Liver Function Tests**

Visit	AST (RR = 0 to 32)	ALT (RR = 0 to 33)	ALP (RR = 35 to 104)	GGT (RR = 6 to 42)	Total Bilirubin (RR = 0 to 1.2)
Screening/Baseline	11.1 U/L	11.7 U/L	96 U/L	17 U/L	0.78 mg/dL
Early Assessment	364.7 U/L	322.7 U/L	107 U/L	14 U/L	0.52 mg/dL
End of Treatment	32.1 U/L	27.9 U/L	158 U/L	10 U/L	0.96 mg/dL
Test of Cure	46.1 U/L	24.4 U/L	212 U/L	17 U/L	1.19 mg/dL

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase;  
GGT = gamma-glutamyl transferase; RR = reference range

**Table 7 Renal Function Tests**

Visit	Blood Urea Nitrogen (RR = 8 to 23)	Serum Creatinine (RR = 0.5 to 0.9)	Creatinine Clearance
Screening/Baseline	88.92 mg/dL	1.46 mg/dL	37.13 mL/min
Early Assessment	98.91 mg/dL	3.08 mg/dL	17.60 mL/min
End of Treatment	44.04 mg/dL	2.07 mg/dL	26.19 mL/min
Test of Cure	9.43 mg/dL	1.18 mg/dL	45.94 mL/min

RR = reference range

**Table 8 Coagulation Tests**

Visit	Platelet Count (RR = 149 to 409)	aPTT (RR = 24 to 35)	PT-INR (RR = 0.8 to 1.2)
Screening/Baseline	$267 \times 10^9/L$	33.5 sec	0.98
Early Assessment	$104 \times 10^9/L$	64.3 sec	3.69
End of Treatment	$97 \times 10^9/L$	75.6 sec	3.83
Test of Cure	$300 \times 10^9/L$	62.1 sec	1.87

aPTT = activated partial thromboplastin time; PT-INR = prothrombin international normalized ratio;  
RR = reference range

## Subject ID Patient # 41

Subject ID	Patient # 41	Country	Israel			
Age	69	Clinical Diagnosis at Screening	BSI			
Gender	Male	Severity	Severe			
Race	White	APACHE II Score	18			
Height (cm)	168	Causative Pathogen at Screening	Pseudomonas aeruginosa			
Body Weight (kg)	90	CR Evidence at Screening (other than central lab)	Blood culture with pseudomonas CR			
MIC of Meropenem	16 µg/mL	MIC of Cefiderocol	1 µg/mL			
MIC of Imipenem	16 µg/mL					
Duration of Study Treatment	15 days	Standard of Care	Ceftazidime (2g q8h IV), ciprofloxacin (400 mg q12h IV)			
Study Drug Treatment	Ceftazidime (2 g q8h IV), ciprofloxacin (400 mg q12h IV)					
Microbiological Results at TOC		Day 28 (EOS) All-cause Mortality	Clinical Outcome at TOC			
Indeterminate		Death (Day 24)	Clinical failure			
Medical History (Ongoing)	Atrial fibrillation permanent, dyslipidemia, rheumatic heart disease, benign hypertrophy of prostate, CHF, hypertension, sleep apnea, prosthetic mitral valve, prosthetic aortic valve, spinal stenosis, permanent pacemaker, anemia, increased GGT, anasarca, hypoalbuminemia, hyperbilirubinemia, increased urea, mechanical ventilation, increased alkaline phosphatase, recurrent bilateral pneumonia, hypomagnesemia, acidosis, increased INR, Enterococcal left subdiaphragmatic abscess, oliguria, sepsis, increased SGOT, hyperglycemia, Staphylococcus capitis bacteremia, hypothermia intermittent, hypophosphatemia, wounds on left abdomen					
Medical History (Not Ongoing)	S/a tricuspid valve repair, cerebrovascular accident, cerebrovascular accident, colon cancer, colectomy transverse colon cancer, rectal bleeding following colectomy to colon cancer, open right hemicolectomy due to ischemic colon, Bacteroides fragilis BSI, fecal peritonitis, ileostomy, peritonitis-Candida glabrata, Candida krusei, Enterococcus, relaparotomy, Citrobacter koseri surgical site infection, Candida BSI, P. pneumonia carbapenem sensitive, stomach ache, vomiting, hypokalemia, renal failure intermittent					
Adverse Event	Day	Severity	Action Taken with Study Drug	Outcome	Causality	Serious
Diarrhea	2	Mild	Dose not changed	Recovered/resolved	Not related	No
Anxiety	3	Mild	Dose not changed	Not recovered/not resolved	Not related	No
Depression	3	Mild	Dose not changed	Unknown	Not related	No
Abdominal pain	3	Mild	Dose not changed	Recovered/resolved	Not related	No
Penile and scrotum wounds	4	Mild	Dose not changed	Unknown	Not related	No

Episodes of hypotension	4	Mild	Dose not changed	Recovered/ resolved	Not related	No
Candiduria	6	Mild	Dose not changed	Recovered/ resolved	Not related	No
Increased creatinine	7	Moderate	Dose reduced	Not recovered/ not resolved	Not related	No
Vomiting	10	Mild	Dose not changed	Recovered/ resolved	Not related	No
Diarrhea	10	Mild	Dose not changed	Recovered/ resolved	Not related	No
Edema left hand	11	Mild	Dose not changed	Recovered/ resolved	Not related	No
Increased WBC	12	Moderate	Dose not changed	Not recovered/ not resolved	Not related	No
Anisocoria	13	Moderate	Dose not changed	Not recovered/ not resolved	Not related	No
Status epilepticus	13	Severe	Drug (ciprofloxacin) withdrawn	Not recovered/ not resolved	Related	Yes
Coffee ground (haematemesis)	14	Mild	Dose not changed	Recovered/ resolved	Not related	No
Melena	14	Mild	Dose not changed	Recovered/ resolved	Not related	No
Right leg erythema	15	Mild	Dose not changed	Recovered/ resolved	Not related	No
Fever	19	Mild	Not applicable	Recovered/ resolved	Not related	No
Low blood pressure	19	Moderate	Not applicable	Recovered/ resolved	Not related	No
General deterioration	24	Severe	Not applicable	Fatal	Not related	Yes

#### Narrative Summary

A 69-year-old white male from Israel with a history of rheumatic heart disease, AF, CHF, and CVA, underwent laparoscopic transverse colectomy for adenocarcinoma of the colon on Day -59. He developed GI bleeding post treatment and was transferred to the ICU on Day -55 and underwent a laparotomy with right colectomy and an ileostomy due to bowel necrosis and fecal peritonitis. He was on mechanical ventilation on Day -55. Blood cultures grew *B. fragilis*. Vancomycin was provided on Day -56. On Day -51, he underwent another laparotomy with debridement. Peritoneal fluid was collected and grew *C. glabrata*, *Enterococcus faecium*, and *C. krusei*. On Day -46 *C. koseri* was reported (surgical site infection). On Day -45, *C. glabrata* grew from blood cultures. He was treated with amphotericin, ciprofloxacin and anidulafungin. On Day -38, he was transferred to the ICU, where he developed *Pseudomonas* pneumonia (Day -19) and was treated with meropenem, with complete resolution.

On Day -14, a CT scan demonstrated a left subphrenic abscess, which was evacuated. *E. faecium* was grown from the abscess, and he was treated with meropenem, which improved his clinical condition and he was transferred to the internal medicine department. On Day -5, he developed septic shock, was transferred back to the ICU with suspected pneumonia, and meropenem was started (Day -5 to Day 1). It was reported that *P. aeruginosa* grew from both respiratory specimens (Day -5 and Day -3) and blood

(Day -3), resistant to carbapenems. On Day -1, he received a single 1000-mg dose of amikacin for the target disease pseudomonas bacteremia. Chest x-rays did not show evidence of pneumonia, and subsequently he was randomized into the study based on the diagnosis of BSI on Day 1.

On Day 1 (Screening/Baseline), a microbiological laboratory specimen was obtained from the tracheal aspirate, and WBC polymorphs (2+, 10 to 24, moderate) and squamous epithelial cells (1+, <10, few) were noted. Gram-negative rods were identified. The pathogen *P. aeruginosa* (no quantitation) was identified at Screening and Baseline (semi-quantitation).

The patient was randomized to treatment with BAT and ceftazidime and ciprofloxacin were started. Treatment with vancomycin 1 g q24h was added from Day -3 to Day -1) due to *S. capitis* bacteremia. Serum creatinine (0.69 mg/dL) at Screening was in the normal range (0.67 to 1.17 mg/dL). He was started on hemofiltration for oliguria and prevention of fluid overload.

On Day 3, EA, microbiological laboratory specimen was obtained from the blood. No gram-negative rods or pathogens were identified. The patient was considered a clinical failure. On Day 4, he completed hemofiltration. Vancomycin 1 g QD was given from Day -3 to Day 6 for *S. capitis* bacteremia. The vancomycin dose was reduced to 500 mg QD from Day 5 to Day 6 due to *S. capitis* bacteremia.

On Day 6, colistin was started. On Day 7, the moderate unrelated AE of increased creatinine (1.47) was reported. The event was considered not related to study treatment. The dose for study treatment was reduced for the event, with no change in the increased creatinine levels. On Day 8, blood cultures from Day 2 showed *Pseudomonas* resistant to ciprofloxacin, and the treating physician changed treatment from ciprofloxacin to colistin, although the response to therapy with ciprofloxacin was good. On the same day, treatment with ciprofloxacin was restarted and therapy with colistin was stopped. On Day 8, vancomycin was restarted and provided until Day 12.

On Day 9, microbiological laboratory specimen obtained from the indwelling urinary catheter showed (colonizer) *Candida parapsilosis* (quantitation,  $> 1 \times 10^5$ ). On Day 12 and Day 13, fluconazole IV was administered to treat candiduria.

On Day 13, he developed the SAE of status epilepticus, which was considered to be related to ciprofloxacin by the investigator, and ciprofloxacin (but not the ceftazidime) was stopped.

On Day 14, creatinine increased to 2.97 mg/dL, and hemodialysis was started due to the increased creatinine levels (indicating renal failure). The ceftazidime dose was reduced from 2 g to 1 g due to increased creatinine from Day 15 to Day 18.

On Day 15, EOT visit was performed; the investigator judged that it could not be ruled out that ceftazidime exacerbated the patient's convulsions. Ceftazidime was continued between Day 15 and Day 18 in error, according to the site. Clinical outcome showed clinical failure. Blood cultures were not performed, as the investigator considered the patient to have successfully improved.

On Day 19, TOC, the clinical outcome was reported as clinical failure with microbiological outcome showing eradication, based on addition of colistin. The blood culture was negative. His serum creatinine (2.76 mg/dL) remained raised and with high serum potassium, of 7.9 mEq/L (RR: 3.5 to 5.2).

His condition continued to deteriorate, he developed (AE) low blood pressure (Day 19), worsening renal function, continuous status epilepticus, and died on Day 24. The investigator felt that the ongoing SAE of general deterioration was the cause of death.

AE = adverse event; AF = atrial fibrillation; APACHE = Acute Physiology and Chronic Health Evaluation; BAT = best available therapy; BSI = blood stream infection; CHF = congestive heart failure; CR = carbapenem resistance; CT = computed tomography; CVA = cerebrovascular accident; EA = Early Assessment; EOS = End of Study; EOT = End of Treatment; GI = gastrointestinal; GGT = gamma glutamyl transferase; ICU = intensive care unit; ID = identification; INR = international normalized ratio; IV = intravenous; MIC = minimum inhibitory concentration; q8h = every 8 hours; q12h = every 12 hours; q24h = every 24 hours; QD = once daily; RR = reference range; s/a =sino atrial; SAE = serious adverse event; SGOT = aspartate transaminase; TOC = Test of Cure; WBC = white blood cell

**Study Qualifying Diagnosis:** Bloodstream infection due to *P. aeruginosa* was identified to be carbapenem resistant through a blood culture.

**Study Qualifying Infection History:** At Day -3, a microbiological laboratory sample obtained from the tracheal aspirate and blood showed *P. aeruginosa* resistant to aztreonam, imipenem, and meropenem. The isolate was susceptible to amikacin, cefepime, ceftazidime-avibactam, ceftolozane-tazobactam, ciprofloxacin, and colistin (Table 3).

**Current Hospitalization History:** The patient was hospitalized from home on an elective basis for a colectomy due to colon cancer on Day -66 and was admitted to the ICU on Day -3 through Day 19. Synchronized intermittent mandatory ventilation (SIMV) was initiated on Day -28 and continued through Day 24. The onset date of the infection was Day -3.

**Clinical Course:** On Day 1 (Screening/Baseline), a microbiological laboratory specimen was obtained from the tracheal aspirate, and WBC polymorphs (2+, 10 to 24, moderate) and squamous epithelial cells (1+, < 10, few) were noted. Gram-negative rods were identified. The pathogen *P. aeruginosa* (semi-quantitation, 2+) was identified. Arterial blood gases (ABGs) indicated PaO<sub>2</sub> of 103 mm Hg, PaCO<sub>2</sub> 50 mm Hg, SaO<sub>2</sub> 98%, and FiO<sub>2</sub> 30%. The initial clinical assessment revealed severe signs and symptoms of the causative infection. The Sequential Organ Failure Assessment (SOFA) score was 8 (Table 2). The inflammatory indices of WBC count, C-reactive protein (CRP), and body temperature were  $7.98 \times 10^9/L$ , 201.24 mg/L, and 36.5°C, respectively (Table 1).

Treatment with BAT (ceftazidime, 2 g IV q8h) was initiated on Day 1. He received 42 subsequent infusions from Day 2 through Day 15. He also received 10 infusions of ciprofloxacin (400 mg IV q12h) on Days 1 through 6 and 10 infusions of ciprofloxacin 200 mg IV q12h on Days 8 through 13. Colistin (2,000,000 U IV q8h) was given from Days 6 to 8.

On Day 2, a microbiological laboratory specimen was also obtained from the blood. The pathogen *P. aeruginosa* (no quantitation) was identified.

On Day 3 (EA), a microbiological laboratory specimen was obtained from the blood. No gram-negative rods or pathogens were identified. The ABGs indicated PaO<sub>2</sub> of 135 mm Hg, PaCO<sub>2</sub> 43 mm Hg, SaO<sub>2</sub> 99%, and FiO<sub>2</sub> 30%. Signs and symptoms revealed moderate signs and symptoms of the causative infection. The SOFA score was 7. The inflammatory indices of WBC count, CRP, and body temperature were  $8.82 \times 10^9/L$ , 167.39 mg/L, and 36.7°C, respectively. The patient was considered a clinical failure.

On Day 6, microbiological laboratory specimens were obtained from the tracheal aspirate, urine (indwelling catheter), and blood. The tracheal aspirate culture contained WBC polymorphs (3+,  $\geq 25$ , many) and squamous epithelial cells (1+, < 10, few). The pathogen *Escherichia coli* (no quantitation, light growth) was identified in the tracheal aspirate. The colonizer *C. parapsilosis* (quantitation,  $> 1 \times 10^5$ ) was identified in the urine and the contaminate *S. capitis* (no quantitation) was identified in the blood.

On Day 7, the patient experienced an AE of increased creatinine of moderate intensity. Study medication was reduced due to the ongoing event (the ciprofloxacin dose was

reduced from 400 mg q12h to 200 mg q12h, and colistin was stopped). The investigator considered the event of increased creatinine not related to study medication.

On Day 9, a microbiological laboratory specimen was obtained from the tracheal aspirate, and WBC polymorphs (3+,  $\geq 25$ , many) and squamous epithelial cells (1+,  $< 10$ , few) were noted. Gram negative rods (4+) were identified. The pathogen *P. aeruginosa* (semi-quantitation, 4+) was identified. A microbiological laboratory specimen was obtained from the urine via an indwelling catheter. The colonizer *C. parapsilosis* (quantitation,  $> 1 \times 10^5$ ) was identified.

On Day 13, a microbiological laboratory specimen was obtained from the tracheal aspirate, and WBC polymorphs (3+,  $\geq 25$ , many) and squamous epithelial cells (1+,  $< 10$ , few) were noted. Gram negative rods (4+) were identified. The pathogen *P. aeruginosa* (semi-quantitation, 4+) was identified. A microbiological laboratory specimen was collected from the urine via an indwelling catheter. The colonizer *C. parapsilosis* (quantitation,  $> 1 \times 10^5$ ) was identified. Another microbiological laboratory sample was obtained from the blood. The contaminate *S. capitis* (no quantitation) was identified.

On Day 13, the patient developed an SAE of status epilepticus of severe intensity, which was felt to be possibly related to study drug (specifically ciprofloxacin) by the investigator. As a result of the event, ciprofloxacin was discontinued.

On Day 14, ABGs indicated PaO<sub>2</sub> of 150 mm Hg, PaCO<sub>2</sub> 36 mm Hg, SaO<sub>2</sub> 99%, and FiO<sub>2</sub> 30%. Signs and symptoms revealed severe signs and symptoms of the causative infection. The SOFA score was 10. The inflammatory indices of WBC, CRP, and body temperature were  $18.23 \times 10^9/L$ , 154.81 mg/L, and 37.5°C, respectively. The patient was considered a clinical failure.

On Day 15 (EOT), no microbiological laboratory specimen was obtained. The patient was considered a clinical failure. The ABGs indicated PaO<sub>2</sub> of 143 mm Hg, PaCO<sub>2</sub> 37 mm Hg, SaO<sub>2</sub> of 99%, and FiO<sub>2</sub> 30%. Signs and symptoms revealed moderate signs and symptoms of the causative infection. The SOFA score was 9. The inflammatory indices of WBC count, CRP, and body temperature were  $13.50 \times 10^9/L$ , 132.89 mg/L, and 36.0°C, respectively (Table 1). The clinical outcome was clinical failure and microbiological outcome was indeterminate, based on use of colistin. Treatment with ceftazidime, 1 g IV q8h continued until Day 18; the ceftazidime dose was reduced from 2 g to 1 g because of increased creatinine from Day 15 to Day 18.

On Day 19 (TOC), a microbiological laboratory specimen was obtained from the blood. Gram-negative rods were not identified. Pulse oximetry indicated SpO<sub>2</sub> 98% and FiO<sub>2</sub> of 50%. Signs and symptoms revealed moderate signs and symptoms of the causative infection. The SOFA score was 15 (Table 2). The inflammatory indices of WBC count, CRP, and body temperature were  $16.54 \times 10^9/L$ , 182.29 mg/L, and 37.5°C, respectively. One dose of amikacin (380 mg IV) was administered on this day. The clinical outcome was clinical failure.

On Day 24, he experienced an SAE of severe general deterioration. No treatment for the event was reported. The outcome of general deterioration was fatal; the patient died on the same day, 9 days after the last dose of study treatment. The investigator considered general deterioration not related to study medication.

**Table 1 Inflammatory Indices**

Visit	White Blood Cell Count (RR = 4 to 10.8)	C-reactive Protein (RR = 0 to 5)	Body Temperature
Screening/Baseline	$7.98 \times 10^9/\text{L}$	201.24 mg/L	36.5°C
Early Assessment	$8.82 \times 10^9/\text{L}$	167.39 mg/L	36.7°C
Day 14	$18.23 \times 10^9/\text{L}$	154.81 mg/L	37.5°C
End of Treatment	$13.50 \times 10^9/\text{L}$	132.89 mg/L	36.0°C
Test of Cure	$16.54 \times 10^9/\text{L}$	182.29 mg/L	37.5°C

RR = reference range

**Table 2 Sequential Organ Failure Assessment Score**

Visit	SOFA Score
Screening/Baseline	8
Early Assessment	7
Day 14	10
End of Treatment	9
Test of Cure	15

SOFA = Sequential Organ Failure Assessment

**Table 3 Antimicrobial Susceptibility Testing at Screening  
(European Committee on Antimicrobial Susceptibility Testing)**

Pathogen	Resistant	Intermediate	Susceptible	Not Applicable
<i>Pseudomonas aeruginosa</i>	Aztreonam, imipenem, meropenem	NA	Amikacin, cefepime, ceftazidime-avibactam, ceftolozane-tazobactam, ciprofloxacin, colistin	Cefiderocol, tigecycline

NA = not applicable

**Table 4 Susceptibility Testing at Each Visit**

Visit	IHMA Organism ID	AMK	AZT	CFPM	CAZ/ AVI	CEF/ TAZ	CPFX	CST	IPM	MEPM	CFDC	TGC
		MIC µg/mL										
Screening/ Baseline	<i>Pseudomonas aeruginosa</i> Sample ID E484169	≤ 4	32	8	8	0.5	0.5	2	16	16	1	> 4
EA Unscheduled 1 Day 2	<i>Pseudomonas aeruginosa</i> Sample ID E590530	≤ 4	32	8	8	1	1	≤ 0.5	32	32	0.12	> 4
Unscheduled 1 Day 9	<i>Pseudomonas aeruginosa</i> Sample ID E590534	≤ 4	32	16	16	1	1	4	16	32	0.25	> 4
Unscheduled Day 13	<i>Pseudomonas aeruginosa</i> Sample ID E736197	≤ 4	32	16	8	1	0.5	4	16	32	0.25	> 4

AMK = amikacin; AZT = aztreonam; CAZ/AVI = ceftazidime-avibactam; CEF/TAZ = ceftolozane-tazobactam; CFDC = cefiderocol; CFPM = cefepime; CPFX = ciprofloxacin; CST = colistin; EA = Early assessment; ID = identification; IHMA = International Health Management Associates; IPM = imipenem; MEPM = meropenem; MIC = minimum inhibitory concentration; TGC = tigecycline

**Table 5 Liver Function Tests**

Visit	AST (RR = 7 to 40)	ALT (RR = 7 to 45)	ALP (RR = 45 to 115)	GGT (RR = 10 to 49)	Total Bilirubin (RR = 0.1 to 1.1)
Screening/Baseline	48 IU/L	7 IU/L	333 IU/L	NA	1.93 mg/dL
Early Assessment	60 IU/L	15 IU/L	429 IU/L	NA	2.02 mg/dL
Day 14	40 IU/L	12 IU/L	313 IU/L	116 IU/L	1.38 mg/dL
End of Treatment	51 IU/L	13 IU/L	407 IU/L	NA	1.71 mg/dL
Test of Cure	38 IU/L	11 IU/L	419 IU/L	NA	2.36 mg/dL

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase;  
GGT = gamma-glutamyl transferase; NA = not available; RR= reference range

**Table 6 Renal Function Tests**

Visit	Blood Urea Nitrogen (RR = 15 to 45)	Serum Creatinine (RR = 0.67 to 1.17)	Creatinine Clearance
Screening/Baseline	26.13 mg/dL	0.69 mg/dL	128.62 mL/min
Early Assessment	16.6 mg/dL	0.47 mg/dL	188.82 mL/min
Day 14	108.74 mg/dL	2.97 mg/dL	NA
End of Treatment	79.8 mg/dL	2.26 mg/dL	39.26 mL/min
Test of Cure	95.8 mg/dL	2.76 mg/dL	NA

NA = not available; RR = reference range

**Table 7 Coagulation Tests**

Visit	Platelet Count (RR = 130 to 440)	aPTT (RR = 24 to 38)	PT-INR (RR = 0.8 to 1.2)
Screening	$243 \times 10^9/L$	37 sec	1.15
Early Assessment	$282 \times 10^9/L$	56 sec	1.17
Day 14	$337 \times 10^9/L$	39 sec	1.47
End of Treatment	$314 \times 10^9/L$	36 sec	1.37
Test of Cure	$378 \times 10^9/L$	41 sec	1.29

aPTT = activated partial thromboplastin time; PT-INR = prothrombin international normalized ratio;  
RR = reference range

## Subject ID Patient # 42

Subject ID	Patient # 42	Country	Korea			
Age	42	Clinical Diagnosis at Screening	VAP			
Gender	Male	Severity	Moderate			
Race	Asian	APACHE II Score	14			
Height (cm)	165.0	Causative Pathogen at Screening	Acinetobacter baumannii			
Body Weight (kg)	55.0	CR Evidence at Screening (other than central lab)	Treatment failure CR-GNB (chromogenic media)			
MIC of Meropenem	64 µg/mL	MIC of Cefiderocol	0.5 µg/mL			
MIC of Imipenem	64 µg/mL					
Duration of Study Treatment	12 days	Standard of Care	Cefepime (6 g IV); Colistin (130 mg IV); Meropenem (0.5 g IV)			
Study Drug	Colistin (65 mg/75 mg/115 mg/130 mg/1.6 vial q12h IV), cefepime (2 g q24h IV), meropenem (0.5 g q24h IV)					
Microbiological Results at TOC		Day 28 All-cause Mortality		Clinical Outcome at TOC		
Indeterminate		Death (Day 13)		Indeterminate		
Medical History (Ongoing)	ESRD, anemia of chronic disease, epilepsy, hypertension, gout, IPMN, pancreas					
Medical History (Not Ongoing)	Tuberculous spondylitis on L1/2; reflux esophagitis; gastritis; PPPD; gastrojejunostomy; abrupt heart arrest, cardiac arrest					
Adverse Events	Day	Severity	Action Taken with Study Drug	Outcome	Causality	Serious
AST increase	9	Moderate	Dose not changed	Recovered/Resolved	Not related	No
Acute respiratory failure	13	Severe	Not applicable	Fatal	Not related	Yes
Abrupt heart arrest	13	Severe	Not applicable	Fatal	Not related	Yes
Narrative Summary						
A 42-year-old Asian male from Korea had a medical history of tuberculous spondylitis on L1/2, ESRD, epilepsy, and hypertension. On Day -64, the patient was hospitalized from home to the general ward due to an IPMN of the pancreas and CAPD. He underwent a PPPD procedure on Day -46. He was transferred to the ICU on Day -45 and placed on mechanical ventilation. A gastrojejunostomy was performed on Day -42, and IPMN of the pancreas with low grade dysplasia (stage and type not specified) was reported. The patient was removed from mechanical ventilation on Day -41 and transferred out of ICU on Day -35. On Day -19, the patient experienced a cardiac arrest and was transferred back to ICU post-ET intubation. Treatment included clindamycin, piperacillin/tazobactam, cefoperazone-sulbactam, and levofloxacin started on Day -14.						

On Day -1, Screening/Baseline, the patient was diagnosed with VAP (onset date of infection Day -8). Chest x-ray showed RLL consolidation. TA culture obtained from ET tube identified *A. baumannii*. A rapid diagnostic test (chromogenic media test) showed evidence of CR in Gram-negative bacilli.

On Day 1, TA culture obtained via ET intubation tube identified *Staphylococcus aureus* (MRSA) and *A. baumannii*. Blood laboratory results showed elevated WBC count, elevated CRP, and elevated creatinine.

The patient was randomized to the BAT arm. BAT/adjunctive treatment included colistin (65 mg/75 mg/115 mg/130 mg/1.6 vial IV q12h) and cefepime (2 g IV q24h) on Day 1 to Day 12 and meropenem (0.5g q24h IV) on Day 4 to Day 12. On Day 4, EA, chest x-ray showed no changes. Intubation tube (ET) culture obtained identified MRSA and *A. baumannii*. The clinical outcome was clinical failure.

On Day 9, the unrelated moderate AE of AST increase was reported. Dose was not changed. It was reported that AST was 99 U/L and the AE of AST increase was considered recovered/resolved on Day 11.

On Day 11, the patient was extubated due to a "Do Not Resuscitate" order. On Day 12, EOT, chest x-ray showed no changes. Sputum culture obtained identified *A. baumannii* and MRSA. Blood laboratory results showed elevated WBC count and CRP. The clinical outcome was clinical failure with microbiological persistence.

On Day 13, the patient experienced the SAEs of acute respiratory failure and abrupt heart arrest. Vasopressin and epinephrine were administered. Blood laboratory results showed elevated WBC count, CRP, potassium, lipase, and AST with an O<sub>2</sub> saturation of 19.6. The ABGs revealed pH at 6.907 (RR 7.35 to 7.45), PO<sub>2</sub> at 24.5 mm Hg (RR 72.0 to 104.0), and PCO<sub>2</sub> at 94.3 mm Hg (RR 35.0 to 48.0). The patient expired at 21:20 hours. The investigator considered the SAEs of acute respiratory failure and abrupt heart arrest to be not related to study drug.

ABG = arterial blood gas; AE = adverse event; APACHE = Acute Physiology and Chronic Health Evaluation; AST = aspartate aminotransferase; BAT = best available therapy; CAPD = continuous ambulatory peritoneal dialysis; CR = carbapenem resistance; CRP = C-reactive protein; EA = Early Assessment; EOT = End of Treatment; ESRD = end-stage renal disease; ET = endotracheal; ICU = intensive care unit; ID = identification; IPMN = intraductal papillary mucinous neoplasm; IV = intravenous; MIC = minimum inhibitory concentration; MRSA = methicillin-resistant *Staphylococcus aureus*; NA = not available; PPPD = pylorus-preserving pancreatoduodenectomy; PT-INR = prothrombin international normalized ratio; q12h = every 12 hours; q24h = every 24 hours; RLL = right lower lung; RR = reference range; SAE = serious adverse event; TA = tracheal aspirate; TOC = Test of Cure; unk = unknown; VAP = ventilator-associated pneumonia; WBC = white blood cell

**Study qualifying diagnosis:** Ventilator-associated pneumonia due to *A. baumannii* was identified to be carbapenem resistant due to treatment failure of CR-GNB using chromogenic media..

**Study qualifying infection history:** On Day -1, *A. baumannii* resistant to amikacin, ciprofloxacin, imipenem, and meropenem was identified from the cultures that were collected from the ET tube. The isolate was susceptible to colistin (Table 3).

**Current hospitalization history:** The patient was hospitalized on Day -64 from home as an emergent admission onto a general ward due to an intraductal papillary mucinous neoplasm of pancreas. The patient was transferred into the ICU on Day -45.

**Clinical course:** On Day -1, a microbiological laboratory sample was obtained from the intubation tube and WBC polymorphs (3+,  $\geq 25$ , many) and squamous epithelial cells (1+,  $< 10$ , few) were noted. The pathogen *A. baumannii* (no quantitation, heavy growth)

was identified. The initial clinical assessment of signs and symptoms showed mild bowel sound, moderate cough, rales, and rhonchi and severe suctioned respiratory secretions.

On Day 1 (Screening/Baseline), a microbiological laboratory sample was obtained from the intubation tube and WBC polymorphs (3+,  $\geq 25$ , many) and squamous epithelial cells (1+,  $< 10$ , few) were noted. Gram-negative rods (+/-) were identified. The pathogens MRSA (no quantitation, heavy growth) and *A. baumannii* (no quantitation, moderate growth) were identified. A chest radiograph showed RLL consolidation (Table 5). The ABG analysis showed PaO<sub>2</sub> at 182 mm Hg, PaCO<sub>2</sub> at 41 mm Hg, SaO<sub>2</sub> at 99%, and FiO<sub>2</sub> at 40%. The Sequential Organ Failure Assessment (SOFA) score was 8, and the Clinical Pulmonary Infection Score (CPIS) was 5 (Table 2). The inflammatory indices of WBC count, CRP, and body temperature were  $19.21 \times 10^9/L$ , 17.9 mg/dL, and 36.9°C, respectively (Table 1). Creatinine was elevated at 4.71 mg/dL (RR 0 to 1.4).

The patient received his first infusion of BAT consisting of colistin 65 mg q12h IV and cefepime 2 g q24h IV on Day 1 and continued through Day 12. Meropenem 0.5g q24h IV was administered on Day 4 through Day 12. Teicoplanin 400 mg q12h IV was also administered.

On Day 4 (EA), a microbiological laboratory sample was obtained from the intubation tubem, and WBC polymorphs (3+,  $\geq 25$ , many) and squamous epithelial cells (2+, 10 to 24, moderate) were noted. Gram-negative rods (+/-) were identified. The pathogens MRSA (no quantitation, heavy growth) and *A. baumannii* (no quantitation, heavy growth) were identified. The chest radiograph showed RLL consolidation. The ABG analysis showed PaO<sub>2</sub> at 99 mm Hg, PaCO<sub>2</sub> at 43 mm Hg, SaO<sub>2</sub> at 97%, and FiO<sub>2</sub> at 40%. Signs and symptoms included moderate cough, rales, and rhonchi, and severe suctioned respiratory secretions. The SOFA score was 8, and the CPIS was 5. The inflammatory indices of WBC count, CRP, and body temperature were  $21.45 \times 10^9/L$ , 13.2 mg/dL, and 37.0°C, respectively. On the same day, the regimen of BAT was changed from colistin 65 mg q12h IV and cefepime 2 g q24h IV to colistin 65/75/115/130 mg q12h IV and 75 mg respiratory inhalation and meropenem 0.5 g q24h IV. The patient was considered a clinical failure.

On Day 11, the patient was extubated because of a “Do Not Resuscitate” order.

On Day 12 (EOT), a microbiological laboratory sample was obtained from the sputum, and WBC polymorphs (3+,  $\geq 25$ , many) and squamous epithelial cells (3+,  $\geq 25$ , many) were noted. Gram-negative rods (+) were identified. The pathogens MRSA (no quantitation, heavy growth) and *A. baumannii* (no quantitation, heavy growth) were identified. A chest radiograph showed persisting RLL pneumonic consolidation. The ABG analysis showed PaO<sub>2</sub> at 139 mm Hg, PaCO<sub>2</sub> at 55 mm Hg, SaO<sub>2</sub> at 98%, and FiO<sub>2</sub> at 40%. Signs and symptoms included mild cough, and moderate rales, rhonchi and suctioned respiratory secretions. The SOFA score was 6, and the CPIS was 6. The inflammatory indices of WBC count, CRP, and body temperature were  $13.73 \times 10^9/L$ , 20.16 mg/dL, and 36.0°C, respectively. The patient was considered a clinical failure with microbiological persistence.

On Day 13, the patient experienced the SAEs of acute respiratory failure and abrupt heart arrest. The patient died due to the events one day after receiving his last dose of BAT. The investigator considered the events severe and not related to study drug.

**Table 1 Inflammatory Indices**

Visit	White Blood Cell Count (RR = 4 to 10)	C-reactive Protein (RR = 0 to 0.3)	Body Temperature
Screening/Baseline	$19.21 \times 10^9/\text{L}$	17.9 mg/dL	36.9°C
Early Assessment	$21.45 \times 10^9/\text{L}$	13.2 mg/dL	37.0°C
End of Treatment	$13.73 \times 10^9/\text{L}$	20.16 mg/dL	36.0°C

RR = reference range

**Table 2 Sequential Organ Failure Assessment and Total Clinical Pulmonary Infection Score Status**

Visit	SOFA Score	Total CPIS
Screening/Baseline	8	5
Early Assessment	8	5
End of Treatment	6	6

CPIS = Clinical Pulmonary Infection Score; SOFA = Sequential Organ Failure Assessment

**Table 3 Antimicrobial Susceptibility Testing at Screening (European Committee on Antimicrobial Susceptibility Testing)**

Pathogen	Resistant	Intermediate	Susceptible	Not Applicable
<i>Acinetobacter baumannii</i>	Amikacin, ciprofloxacin, imipenem, meropenem	NA	Colistin	Aztreonam, cefepime, ceftazidime-avibactam, ceftolozane-tazobactam, cefiderocol, tigecycline

NA = not applicable

**Table 4 Susceptibility Testing at Each Visit**

Visit	IHMA Organism ID	AMK	AZT	CFPM	CAZ/AVI	CEF/TAZ	CPFX	CST	IPM	MEPM	CFDC	TGC
		MIC µg/mL										
Screening/ Baseline	<i>Acinetobacter baumannii</i> Sample ID E797583	> 64	32	> 16	16	16	> 4	2	64	64	0.5	0.5
Early Assessment	<i>Acinetobacter baumannii</i> Sample ID E797581	> 64	32	> 16	16	16	> 4	1	64	64	0.06	1
End of Treatment	<i>Acinetobacter baumannii</i> Sample ID E797582	> 64	32	> 16	16	16	> 4	1	64	64	0.12	1

AMK = amikacin; AZT = aztreonam; CAZ/AVI = ceftazidime-avibactam; CEF/TAZ = ceftolozane-tazobactam; CFDC = cefiderocol; CFPM = cefepime; CPFX = ciprofloxacin; CST = colistin; ID = identification; IHMA = International Health Management Associates; IPM = imipenem; MEPM = meropenem; MIC = minimum inhibitory concentration; TGC = tigecycline

**Table 5 Chest Radiograph Results**

Visit	Lung Fields/ Airways	Heart/ Vessels	Other Structures	Comparison of Lung Fields to Screening
Day -1	RLL consolidation	Normal	Normal	NA
Early Assessment	RLL consolidation	Normal	Normal	No change
End of Treatment	Persisting RLL pneumonic consolidation	Normal	Normal	No change

NA = not available; RLL = right lower lung

**Table 6 Liver Function Tests**

Visit	AST (RR = 0 to 40)	ALT (RR = 0 to 40)	ALP (RR = 0 to 190)	GGT (RR = 0 to 60)	Total Bilirubin (RR = 0 to 1.3)
Screening/Baseline	23 U/L	< 4 U/L	172 U/L	57 U/L	0.56 mg/dL
Early Assessment	23 U/L	5 U/L	126 U/L	51 U/L	0.48 mg/dL
End of Treatment	65 U/L	10 U/L	213 U/L	51 U/L	0.92 mg/dL

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase;  
GGT = gamma-glutamyl transferase; RR = reference range

**Table 7 Renal Function Tests**

Visit	Blood Urea Nitrogen (RR = 0 to 20)	Serum Creatinine (RR = 0 to 1.4)	Creatinine Clearance
Screening/Baseline	26.3 mg/dL	4.71 mg/dL	15.89 mL/min
Early Assessment	34.7 mg/dL	4.03 mg/dL	18.58 mL/min
End of Treatment	33.4 mg/dL	2.73 mg/dL	27.42 mL/min

NA = not available; RR = reference range

**Table 8 Coagulation Tests**

Visit	Platelet Count (RR = 165 to 360)	aPTT (RR = 23.6 to 30.9)	PT-INR (RR = 0.92 to 1.13)
Screening/Baseline	$82 \times 10^9/L$	34.2 sec	1.39
Early Assessment	$118 \times 10^9/L$	32.6 sec	1.40
End of Treatment	$147 \times 10^9/L$	82.0 sec	1.37

aPTT = activated partial thromboplastin time; PT-INR = prothrombin international normalized ratio;  
RR = reference range

### Subject ID Patient # 43

Subject ID		Patient #43	Country		South Korea	
Age		62	Clinical Diagnosis at Screening		cUTI	
Gender		Male	Severity		Severe	
Race		Asian	APACHE II Score		13	
Height (cm)		173.0	Causative Pathogen at Screening		Pseudomonas aeruginosa	
Body Weight (kg)		50.0	CR Evidence at Screening (other than central lab)		Treatment failure CR-GNB Xpert Carba-R	
MIC of Meropenem		> 64 µg/mL	MIC of Cefiderocol		2 µg/mL	
MIC of Imipenem		32 µg/mL				
Duration of Study Treatment		6 days	Standard of Care		Colistin (150 mg, IV)	
Study Drug		BAT (colistin 150 mg, IV, q12h)				
Microbiological Results at TOC			Day 28 All-cause Mortality		Clinical Outcome at TOC	
Indeterminate			Death (Day 6)		Clinical failure	
Medical History (Ongoing)	Alcoholic dementia, both bed sore, hypokalemia, thrombocytopenia, constipation, hypomagnesemia, hypocalcemia, hypophosphatemia, right ureter stone, hypoalbuminemia, anemia, tinea pedis, septic shock, stress induced cardiomyopathy, alcoholic liver cirrhosis, hydronephrosis, lactic acidosis, xerotic eczema, liver enzyme elevation; pulmonary edema					
Medical History (Not Ongoing)	Leukopenia					
Adverse Event	Day	Severity	Action Taken with Study Drug	Outcome	Causality	Serious
Catheter-related infection	2	Severe	Dose not changed	Fatal	Not related	Yes
Aggravated septic shock	6	Severe	Dose not changed	Fatal	Not related	Yes
Narrative Summary						
A 62-year-old Asian male from South Korea had a history of alcoholic dementia and bed sores of both heels.						
On Day -123, the patient was admitted to the general ward from a skilled nursing facility due to alcoholic dementia, and on Day -7, he was then transferred (with indwelling catheter in place) to the site hospital due to hypothermia (34.5°C) and oliguria. It was reported that urine volume decreased and he developed generalized edema 2 days before. Alcoholic liver cirrhosis, thrombocytopenia, anemia, and lactic acidosis with a level of 2.3 was reported by the investigator. A CT of the abdomen showed a right ureter stone with right hydronephrosis. He was diagnosed to have septic shock due to acute pyelonephritis caused by multidrug-resistant <i>P. aeruginosa</i> . Meropenem (1 g q24h) and ceftriaxone (2 g q24h) IV were started. A CVC was inserted for volume status monitoring. On Day -4, the patient was transferred to the ICU and inotropics (norepinephrine) were provided. Liver enzyme elevation was reported on Day -4. On Day -3, ertapenem was given.						
On Day -1, the patient was enrolled in the study, based on treatment failure CR-GNB pathway. Urine specimen showed evidence of CR-GNB with Xpert Carba-R. Urine culture obtained from the indwelling						

catheter was positive for *P. aeruginosa* ( $> 1 \times 10^5$ ). Clinical signs and symptoms included moderate suprapubic/flank/back pain (temperature was 38.0°C). Blood sample results showed a normal WBC count. Urine results showed 3+ urine occult blood and trace urine protein; urine sediment WBC showed many/HPF.

On Day 1, the patient was randomized to the BAT arm. Colistin 150 mg IV was provided q12h until Day 6.

On Day 2, the SAE of catheter-related infection was reported; study drug dose was not changed. Coagulase-negative *Staphylococcus* was identified as the pathogen on Day 6.

On Day 4, EA was performed. Clinical assessment showed moderate suprapubic/flank/back pain. Urine culture obtained from the indwelling catheter was positive for *P. aeruginosa* ( $> 1 \times 10^5$  CFU/mL). Blood culture collected on Day 4 showed MRSA. Clinical and microbiological outcomes were assessed as clinical failure and indeterminate, respectively. Vancomycin 1g q12h was given on Day 5.

The patient died due to aggravated septic shock and the catheter-related infection on Day 6. The investigator considered the events not related to the study medication.

APACHE = Acute Physiology and Chronic Health Evaluation; BAT = best available therapy; CFU = colony forming units; CR = carbapenem resistance; CT = computed tomography; cUTI = complicated urinary tract infection; CVC = central venous catheter; EA = Early Assessment; GNB = Gram-negative bacteria; HPF = high power field; ICU = intensive care unit; ID = identification; IV = intravenous; MIC = minimum inhibitory concentration; MRSA = methicillin-resistant *Staphylococcus aureus*; NA = not available; q12h = every 12 hours; q24h = every 24 hours; SAE = serious adverse event; TOC = Test of Cure; unk = unknown; WBC = white blood cell

**Study qualifying diagnosis:** Complicated urinary tract infection due to *P. aeruginosa* identified to be carbapenem resistant through treatment failure and CR-GNB pathway.

**Study qualifying infection history:** On Day 1, *P. aeruginosa* resistant to amikacin, aztreonam, cefepime, ceftazidime-avibactam, ceftolozane-tazobactam, ciprofloxacin, imipenem, and meropenem was identified from the urine via an indwelling catheter (Table 3). The isolate was susceptible to colistin.

In parallel with this identification, the patient was treated with colistin (150 mg, IV, q12h).

**Current hospitalization history:** The patient was transferred on Day -4 from a clinic as an emergent admission onto the ICU due to cUTI. The onset date of the infection was Day -9. The patient was previously hospitalized from a skilled nursing facility as an elective admission to a general ward due to alcoholic dementia.

**Clinical course:** On Day -1 (Screening/Baseline), a microbiological sample was obtained from the urine via an indwelling catheter. Gram-negative rods (6+) were identified. The pathogen *P. aeruginosa* (quantitation,  $> 1.0 \times 10^5$ ) was identified. The initial clinical assessment of signs and symptoms showed moderate suprapubic/flank/back pain. The Sequential Organ Failure Assessment (SOFA) score was 6 (Table 2). The inflammatory indices of WBC count, C-reactive protein (CRP), and body temperature were  $7.47 \times 10^9/L$ , 8.67 mg/dL, and 38.0°C, respectively (Table 1).

On Day 1, a microbiological sample was obtained from the urine via an indwelling catheter. Gram-negative rods (6+) were identified. The pathogen *P. aeruginosa* (quantitation,  $> 1.0 \times 10^5$ ) was identified.

The patient received his first dose of BAT consisting of colistin (150 mg, IV, q12h) on Day 1 and received 10 subsequent doses of colistin (150 mg, IV, q12h) through Day 6.

On Day 2, the patient experienced the SAE of catheter-related infection. Coagulase-negative *Staphylococcus* was reported as the pathogen on Day 6. The dose of study medication was not changed. Treatment included vancomycin and meropenem. The investigator considered the event severe and not related to the study medication.

On Day 4 (EA), a microbiological sample was obtained from the urine via indwelling catheter. Gram-negative rods (6+) were identified. The pathogen *P. aeruginosa* (quantitation,  $> 1.0 \times 10^5$ ) was identified. A microbiological sample was also obtained from the blood. The pathogen MRSA was identified. Signs and symptoms included moderate suprapubic/flank/back pain, and no new signs of infection occurred since baseline. The SOFA score was 6 (Table 2). The inflammatory indices of WBC count, CRP, and body temperature were  $6.91 \times 10^9/L$ , 15.46 mg/dL, and 37.3°C, respectively (Table 1). The blood lab results showed activated partial thromboplastin time (aPTT) 56.9 seconds (reference range [RR] 20 to 38) and total bilirubin 1.95 mg/dL (RR 0.2 to 1.2). The patient was considered a clinical failure with indeterminate microbiological outcome.

Blood culture collected on Day 4 showed MRSA. Vancomycin (1 g, IV, q24h) was given on Day 5.

On Day 6 (End of Study/End of Treatment), the body temperature was 35.9°C. The patient experienced the SAE of aggravated septic shock. The dose of study medication was not changed. Treatment included hydrocortisone (100 mg, IV, q12h), norepinephrine, vasopressin, and epinephrine. The investigator considered the event severe and not related to the study medication. The patient died due to the SAE of catheter-related infection (the catheter was a CVC inserted for septic shock) and aggravated septic shock the same day he received his last dose of study medication.

**Table 1 Inflammatory Indices**

Visit	White Blood Cell Count (RR = 4 to 10)	C-reactive Protein (RR = 0 to 0.5)	Body Temperature
Screening/Baseline	$7.47 \times 10^9/L$	8.67 mg/dL	38.0°C
Early Assessment	$6.91 \times 10^9/L$	15.46 mg/dL	37.3°C
End of Treatment/ End of Study	NA	NA	35.9°C

NA = not available; RR = reference range

**Table 2 Sequential Organ Failure Assessment**

Visit	SOFA Score
Screening/Baseline	6
Early Assessment	6

SOFA = Sequential Organ Failure Assessment

**Table 3 Antimicrobial Susceptibility Testing at Screening  
(European Committee on Antimicrobial Susceptibility Testing)**

Pathogen	Resistant	Intermediate	Susceptible	Not Applicable
<i>Pseudomonas aeruginosa</i>	Amikacin, aztreonam, cefepime, ceftazidime-avibactam, ceftolozane-tazobactam, ciprofloxacin, imipenem, meropenem	NA	Colistin	Cefiderocol, tigecycline

NA = not available

**Table 4 Susceptibility Testing at Each Visit**

Visit	IHMA Organism ID	AMK	AZT	CFPM	CAZ/ AVI	CEF/ TAZ	CPFX	CST	IPM	MEPM	CFDC	TGC
		MIC µg/mL										
Screening/ Baseline	<i>Pseudomonas aeruginosa</i> Sample ID E773749	> 64	32	> 16	> 64	> 64	> 4	1	32	> 64	2	> 4
Early Assess- ment	<i>Pseudomonas aeruginosa</i> Sample ID E773745	> 64	32	> 16	> 64	> 64	> 4	1	32	> 64	2	> 4

AMK = amikacin; AZT = aztreonam; CAZ/AVI = ceftazidime-avibactam; CEF/TAZ = ceftolozane-tazobactam; CFDC = cefiderocol; CFPM = cefepime; CPFX = ciprofloxacin; CST = colistin; ID = identification; IHMA = International Health Management Associates; IPM = imipenem; MEPM = meropenem; MIC = minimum inhibitory concentration; NA = not available; TGC = tigecycline

**Table 5 Liver Function Tests**

Visit	AST (RR = 0 to 34)	ALT (RR = 10 to 49)	ALP (RR = 45 to 129)	GGT (RR = 16 to 73)	Total Bilirubin (RR = 0.2 to 1.2)
Screening/Baseline	28 U/L	23 U/L	68 U/L	22 U/L	0.85 mg/dL
Early Assessment	13 U/L	9 U/L	52 U/L	14 U/L	1.95 mg/dL

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase;  
GGT = gamma-glutamyl transferase; RR = reference range

**Table 6 Renal Function Tests**

Visit	Blood Urea Nitrogen (RR = 9 to 23)	Serum Creatinine (RR = 0.7 to 1.3)	Creatinine Clearance
Screening/Baseline	12 mg/dL	0.20 mg/dL	270.83 mL/min
Early Assessment	17 mg/dL	0.22 mg/dL	246.21 mL/min

RR = reference range

**Table 7 Coagulation Tests**

Visit	Platelet Count (RR = 130 to 400)	aPTT (RR = 20 to 38)	PT-INR (RR = 0 to 1)
Screening/Baseline	$124 \times 10^9/\text{L}$	38.7 sec	1.19
Early Assessment	$282 \times 10^9/\text{L}$	56.9 sec	1.40

aPTT = activated partial thromboplastin time; PT-INR = prothrombin international normalized ratio;  
RR = reference range

## 15.8 Appendix 8 – Compassionate Use Summary Information by Patient

Patient/ Country	Age/ Gender	Relevant Medical History	Infection Type	Causative Pathogen	Concomitant Antibiotics	Cefiderocol Dose and Regimen	Duration Cefiderocol Treatment, days	Reported SAEs	Patient Outcome
Case 1/ USA	8 y/ Female	Born with meconium peritonitis with perforated intestine leading to liver and small intestine transplantation; parenteral nutrition since birth; continuous hemodialysis	BSI	<i>Pseudomonas aeruginosa</i>	Ceftolozane/tazobactam, colistin, tigecycline, meropenem, doripenem	750 mg q8h over 3 hours (6 days) 1500 mg q8h over 3 hours (7 days)	15	Hemorrhage and pancreatitis (physician assessed both as unrelated to cefiderocol)	No positive blood cultures were reported after 7 days of cefiderocol treatment. However, the ultimate outcome was death due to internal bleeding at the anastomosis site between transplanted organs and blood vessel.
Case 2/ UK	56 y/ Male	Renal transplantation; urosepsis	Discitis (T12/L1)	<i>Pseudomonas aeruginosa</i> <i>Leuconostoc pseudomesenteroides</i> <i>Parvimonas micra</i>	Clindamycin, colistin, metronidazole, amoxicillin	2000 mg q8h over 3 hours (55 days) 2000 mg q8h over 3 hours (31 days) 2000 mg q8h over 3 hours (8 days)	94	None reported	Recovered

Patient/ Country	Age/ Gender	Relevant Medical History	Infection Type	Causative Pathogen	Concomitant Antibiotics	Cefiderocol Dose and Regimen	Duration Cefiderocol Treatment, days	Reported SAEs	Patient Outcome
Case 3/ Israel	62 y/ Female	Subject initially in CREDIBLE-CR study and randomized to BAT (Subject (b) (6)) Carcinoma of ovaries with metastasis for intra-abdominal surgery	BSI	<i>Acinetobacter baumannii</i> <i>Geotrichum candidum</i> <i>Enterococcus faecalis</i>	Colistin, amphotericin, meropenem, imipenem, tigecycline, fluconazole, voriconazole	750 mg q12h + extra dose after dialysis (15 days) 1500 mg q8h (20 days)	35	Cardio- respiratory arrest	Developed severe thrombocyto- penia, which did not respond to platelet infusion, and had more leakage from the intestine and died.
Case 4/ USA	25 y/ Female	Cystic fibrosis, double lung transplant, distal intestinal obstruction syndrome, pancreatic insufficiency, multidrug resistant <i>Burkholderia cenocepacia</i>	Respiratory infection	<i>Burkholderia cenocepacia</i>	Minocycline, meropenem, levofloxacin, sulfamethox-azole/ trimethoprim	2000 mg q8h (3 days) 1500 mg q8h (2 days) 2000 mg q8h (2 days) 1500 mg q12h (1 day)	8	Respiratory failure (physician assessed as unrelated to cefiderocol)	Died due to sepsis caused by <i>Burkholderia</i> infection.

Patient/ Country	Age/ Gender	Relevant Medical History	Infection Type	Causative Pathogen	Concomitant Antibiotics	Cefiderocol Dose and Regimen	Duration Cefiderocol Treatment, days	Reported SAEs	Patient Outcome
Case 5/ USA	75 y/ Male	<i>Escherichia coli</i> and <i>Methicillin-sensitive Staphylococcus aureus</i> infected prosthetic hip explant and developed postoperative surgical infection	Infection of prosthetic hip explant, urinary tract infection, and pneumonia	<i>Acinetobacter baumannii</i>	Ampicillin/sulbactam	1000 mg q8h over 3 hours (9 days) 1500 mg q8h over 3 hours (32 days [missed 2 days])	41	None	No active infection was found at the time of discharge to hospice. Death occurred at home (23 days after last dose of cefiderocol).
Case 6/ UK	78 y/ Female	Atrial fibrillation, aortic stenosis, ischemic heart, hydronephrosis, urosepsis, heparin-induced thrombocytopenia	Bacteremia due to cUTI, aortic valve endocarditis	<i>Pseudomonas aeruginosa</i>	Colistin; meropenem IV	3000 mg q8h over 3 hours (1 day) 2000 mg q12h over 3 hours (30 days)	31	Acute neutropenia	Blood cultures were negative following cefiderocol treatment prior to valve replacement and no positive culture was obtained from the surgically removed heart valve. Patient remained clinically stable.

Patient/ Country	Age/ Gender	Relevant Medical History	Infection Type	Causative Pathogen	Concomitant Antibiotics	Cefiderocol Dose and Regimen	Duration Cefiderocol Treatment, days	Reported SAEs	Patient Outcome
Case 7/ Spain	66 y/ Male	Ischemic cardiomyopathy with severe left ventricle dysfunction; resynchroniz- ation therapy device implanted; lung adenocarcinoma; left ventricular assist system implanted as destination therapy	Bacteremia associated with implanted cardiac device	<i>Achromo- bacter xylosoxidans</i>	Piperacillin/ tazobactam, tigecycline	2000 mg q8h over 3 hours	11	Moderate thrombocyte- penia	Without fever, with negative blood cultures and with good clinical conditions; Receiving oral suppressive therapy with minocycline.

Patient/ Country	Age/ Gender	Relevant Medical History	Infection Type	Causative Pathogen	Concomitant Antibiotics	Cefiderocol Dose and Regimen	Duration Cefiderocol Treatment, days	Reported SAEs	Patient Outcome
Case 8/ Italy	54 y/ Female	Orthotopic liver transplant; allergic asthma, thalassemic trait, cholecystectomy, liver cirrhosis secondary to sclerosing cholangitis, history of portal vein thrombosis, and cavernous transformation of the portal vein	BSI	<i>Acinetobacter baumannii</i>	Meropenem, tigecycline, colistin, anidula- fungin, rifampicin, amphotericin B liposome	1000 mg q12h over 3 hours (40 days)	40	Cardiac arrest (assessed as not related to cefiderocol by the physician)	Following an initial recovery and negative microbiology samples after 9 days of cefiderocol treatment, at Day 16, septic shock occurred and did not respond to therapy. She developed multiorgan failure and died of cardiac arrest 1 day after stopping cefiderocol.

Patient/ Country	Age/ Gender	Relevant Medical History	Infection Type	Causative Pathogen	Concomitant Antibiotics	Cefiderocol Dose and Regimen	Duration Cefiderocol Treatment, days	Reported SAEs	Patient Outcome
Case 10/ Italy	73 y/ Male	Severe respiratory insufficiency under invasive ventilation secondary to hospital-acquired pneumonia; rhinopharyngeal cancer; polyneuropathic myopathy; cachexia, anorexia; HSV-1 encephalitis	Hospital- acquired pneumonia	<i>Acinetobacter baumannii</i> , <i>Pseudomonas aeruginosa</i> , and methicillin- sensitive <i>Staphylococ- cus aureus</i>	Tigecycline, colistin, ampicillin/ sulbactam, voriconazole	2000 mg q8h over 3 hours (4 days)	4	Severe respiratory failure (physician assessed as not related to cefiderocol), multiple organ failure, pancytopenia, acute pancreatitis, and acute renal failure (assessed by physician as not related to cefiderocol)	Patient went into coma, followed by decline in cognitive function and clinical conditions worsened. Patient died (treating physician assessed as not related to cefiderocol) after stopping cefiderocol.

Patient/ Country	Age/ Gender	Relevant Medical History	Infection Type	Causative Pathogen	Concomitant Antibiotics	Cefiderocol Dose and Regimen	Duration Cefiderocol Treatment, days	Reported SAEs	Patient Outcome
Case 11/ Italy	14 mo/ Male	Severe aplastic anemia, infection in appendicular region	Periappen- dicular region infection	MDR <i>Pseudomonas aeruginosa</i>	Ceftolozane/ tazobactam, aztreonam, amikacin, fosfomycin	720 mg q8h (each given as a 3-hour infusion) (62 days)	62	Pyrexia (physician assessed as not related to cefiderocol)	During treatment with cefiderocol, patient successfully underwent appendectomy and surrounding necrotic tissue removal, followed by bone marrow transplanta-tion; discharged 1 month after last dose of cefiderocol; patient was in excellent condition, with no graft versus host disease signs.

Patient/ Country	Age/ Gender	Relevant Medical History	Infection Type	Causative Pathogen	Concomitant Antibiotics	Cefiderocol Dose and Regimen	Duration Cefiderocol Treatment, days	Reported SAEs	Patient Outcome
Case 13/ USA	69 y/ Female	Lung transplant complicated by empyema, multilevel rib osteomyelitis, kidney injury, and steroid-induced diabetes	Chest wall soft tissue infection	MDR <i>Pseudomonas aeruginosa</i>	Vancomycin, sulfamethoxazole/trimethoprim, valganciclovir	1000 mg q8h (56 days)	56	None reported	Recovered and discharged home.
Case 14/ USA	69 y/ Female	Necrotizing pneumonia, complicated by respiratory failure	Pneumonia	<i>Pseudomonas aeruginosa</i> ; <i>Stenotrophomonos maltophilia</i>	Sulfamethoxazole/trimethoprim, tobramycin, piperacillin/tazobactam, ciprofloxacin	Dosage not specified (14 days)	14	None reported	Recovered and discharged home.
Case 15/ USA	36 y/ Male	Acute lymphocytic leukemia, bone marrow transplant, chronic lung disease, coronary artery disease, asthma	Pneumonia	<i>Burkholderia cepacia</i>	Trimethoprim/sulfamethoxazole, ceftazidime/avibactam, azithromycin	2000 mg q8h over 3 hours (5 days)	5	None reported	Recent microbiology samples were negative and discharged to long-term care facility.

Patient/ Country	Age/ Gender	Relevant Medical History	Infection Type	Causative Pathogen	Concomitant Antibiotics	Cefiderocol Dose and Regimen	Duration Cefiderocol Treatment, days	Reported SAEs	Patient Outcome
Case 16/ USA	22 y/ Male	Cystic fibrosis, lung transplant, respiratory failure, leukopenia, post- transplant chest wall and bloodstream infection	Chest wall and BSI	<i>Burkholderia cepacia</i>	Vancomycin, levofloxacin, meropenem, metronida- zole, minocycline, septra, tedizolid, tobramycin	2000 mg q8h over 3 hours (19 days) 1500 mg q12h over 3 hours (2 days)	21	Sepsis (physician assessed as unrelated to cefiderocol)	Died due to <i>Burkholderia</i> bacteremia refractory to multiple agents.
Case 17/ USA	37 y/ Male	Cystic fibrosis, bilateral lung transplant, bronchiolitis obliterans, graft dysfunction, acute cellular rejection, hypercapnic respiratory failure, end stage renal disease	<i>Burkhold- eria</i> lung infection	<i>Burkholderia multivorans</i> <i>Burkholderia cepacia</i> <i>Pseudomonas aeruginosa</i>	Tobramycin, ceftazidime, avibactam, cotrimoxa- zole, minocycline, meropenem	Dosage not specified (2 days)	2	Progression of underlying pneumonia (physician assessed as unrelated to cefiderocol)	Died due to progression of underlying pneumonia.
Case 18/ USA	28 y/ Male	Cystic fibrosis post lung transplant and septic shock	BSI	<i>Achromobac- ter species</i>	Piperacillin/ tazobactam, imipenem, doxycycline	2000 mg q8h over 8 hours (28 days with a 14- day break followed by 42 days)	70	Chylothorax (physician assessed as unrelated to cefiderocol)	After discharge, patient developed cough and shortness of breath and was readmitted and again treated with cefiderocol. Patient reported as doing well.

Patient/ Country	Age/ Gender	Relevant Medical History	Infection Type	Causative Pathogen	Concomitant Antibiotics	Cefiderocol Dose and Regimen	Duration Cefiderocol Treatment, days	Reported SAEs	Patient Outcome
Case 20/ USA	67 y/ Male	Post heart transplant due to ischemic heart disease; had lung transplant and developed complications including pneumothoraces	Respiratory infection	<i>Acinetobacter baumannii</i>	Inhaled colistin	1500 mg q12h over 3 hours (32 days with a 2-day break followed by 11 days)	43	None reported	Recurrence of <i>A. baumannii</i> and patient died.
Case 21/ USA	77 y/ Male	Ruptured abdominal aortic aneurysm, prolonged hospitalization, possible endocarditis and sternal osteomyelitis	BSI	MDR <i>Acinetobacter baumannii</i>	None reported	750 mg q12h over 3 hours (3 days)	3	Multiorgan failure with a fatal outcome (physician assessed as unrelated to cefiderocol)	Worsening pleural effusion on same day as starting cefiderocol; patient underwent tracheostomy exchange and condition deteriorated. Family opted for comfort care, and patient died.

Patient/ Country	Age/ Gender	Relevant Medical History	Infection Type	Causative Pathogen	Concomitant Antibiotics	Cefiderocol Dose and Regimen	Duration Cefiderocol Treatment, days	Reported SAEs	Patient Outcome
Case 22/ USA	35 y/ Male	MDR <i>Acinetobacter</i> following ICU care for polymicrobial septic shock	Respiratory and BSI	MDR <i>Acinetobacter</i> <i>calcoaceti-</i> <i>cus/</i> <i>baumannii</i>	Cefepime, oral vancomycin, tigecycline, inhaled colistin, polymyxin	2000 mg q8h over 3 hours (14 days with a 6-day break followed by 6 days)	20	LFT abnormality LFTs mildly elevated prior to cefiderocol; reporting physician assessed the elevated AST/ALT as possibly related to cefiderocol and concomitant treatments and ALK as not related to cefiderocol. LFTs worsened after restarting cefiderocol Discontinued cefiderocol due to worsening LFTs; continued to increase after discontinuation.	Recovered and returned home. 4 months after cefiderocol, he had MSSA bacteremia, developed septic shock, and died.

Patient/ Country	Age/ Gender	Relevant Medical History	Infection Type	Causative Pathogen	Concomitant Antibiotics	Cefiderocol Dose and Regimen	Duration Cefiderocol Treatment, days	Reported SAEs	Patient Outcome
Case 23/ USA	51 y/ Male	HIV (recently diagnosed), pancytopenia, diffuse B cell lymphoma, <i>Acinetobacter</i> on blood culture from line infection	BSI	MDR <i>Acinetobacter baumannii</i>	Vancomycin, cefepime, polymyxin B, tigecycline	1500 mg q12h over 3 hours (2 days)	2	Septic shock with bacteremia that resulted in death; assessed as not related to cefiderocol by treating physician and instead related to <i>Acinetobacter</i>	Family decided patient should only receive symptomatic care; patient died same day due to septic shock due to <i>Acinetobacter</i> .
Case 24/ Israel	5 mo/ Male	Heart transplantation, hypertrophic cardiomyopathy due to multiple rhabdomyomas, bilateral lung consolidation, kidney failure with CRRT	BSI	MSSA and MDR <i>Acinetobacter baumannii</i>	Cefamezine, tigecycline, colistemetate	300 mg (60 mg/kg) q8h over 3 hours (2 days)	2	Fatal outcome (death) reported with deterioration of current clinical condition	Patient died after receiving 2 doses of cefiderocol. Treating physician noted patient was unstable when received cefiderocol and death was not related to cefiderocol.
Case 26/ USA	67 y/ Male	Prostate cancer, B cell lymphoblastic leukemia, neutropenia, and MDR <i>Pseudomonas aeruginosa</i>	BSI	MDR <i>Pseudomonas aeruginosa</i>	Ceftolozane/ tazobactam, polymyxin B, ciprofloxacin	1500 mg TID (16 days)	16	None reported	Patient was discharged to rehabilitation.

Patient/ Country	Age/ Gender	Relevant Medical History	Infection Type	Causative Pathogen	Concomitant Antibiotics	Cefiderocol Dose and Regimen	Duration Cefiderocol Treatment, days	Reported SAEs	Patient Outcome
Case 27/ France	63 y/ Female	Pulmonary fibrosis, right lung transplant; chronic renal failure, hypertension, diabetes mellitus, and left ventricular hypotrophy	Pulmonary abscess	<i>Pseudomonas aeruginosa</i>	Colistime-thate sodium	1500 mg TID (15 days) with a 6-day break then 1000 mg TID over 3 hours (18 days)	33	Acute kidney injury, was assessed by the treating physician as related to colistimethate sodium but could not rule out relationship with cefiderocol	Patient died of uncontrolled sepsis due to multiorgan failure.
Case 28/ USA	46 y/ Female	Pseudomonal intra-abdominal abscess as a complication of gastric band surgery	BSI	MDR <i>Pseudomonas aeruginosa</i>	Cefepime, colistin, metronidazole	2000 mg q8h over 3 hours (15 days)	15	None reported	Abscess resolved, fistula closed, and patient was discharged home.
Case 29/ USA	56 y/ Female	Cystic fibrosis and <i>Achromobacter</i> pneumonia; lung transplant and postoperative <i>Achromobacter</i> empyema	Respiratory infection	<i>Achromobacter</i>	Piperacillin-tazobactam, colistin	2000 mg q8h over 3 hours (2 days with a 59-day break followed by 13 days)	15	None reported	Patient improved and moved to rehabilitation.

Patient/ Country	Age/ Gender	Relevant Medical History	Infection Type	Causative Pathogen	Concomitant Antibiotics	Cefiderocol Dose and Regimen	Duration Cefiderocol Treatment, days	Reported SAEs	Patient Outcome
Case 33/ USA	68 y/ Female	Intra-abdominal <i>Klebsiella pneumoniae</i> infection post renal transplant for end stage renal disease	BSI	<i>Klebsiella pneumoniae</i>	Ceftazidime/ avibactam, aztreonam, polymyxin B, plazomycin	1500 mg q12h over 3 hours (13 days)	13	None reported	Prognosis was deemed poor, and family decided to withdraw care.
Case 34/ USA	75 y/ Male	Mechanical fall that resulted in T1-T6 fracture complicated by infection	Hardware infection	<i>Acinetobacter baumannii</i>	No concomitant antibiotics reported	2000 mg q8h over 3 hours (39 days)	39	None reported	Reported as doing well and discharged home.
Case 35/ USA	82 y/ Male	Cholangio- carcinoma, polymicrobial liver abscess, chronic kidney disease	BSI	MDR <i>Pseudomonas aeruginosa</i>	Polymyxin B, meropenem, rifampicin	1000 mg q8h over 3 hours (14 days)	14	None reported	Family decided to discontinue cefiderocol and move patient to hospice care due to ongoing oncological issues.

Patient/ Country	Age/ Gender	Relevant Medical History	Infection Type	Causative Pathogen	Concomitant Antibiotics	Cefiderocol Dose and Regimen	Duration Cefiderocol Treatment, days	Reported SAEs	Patient Outcome
Case 38/ USA	17 y/ Female	Cystic fibrosis, listed for transplant and colonized with <i>Achromobacter</i>	Lung infection	<i>Achromo- bacter xylosoxidans</i>	IV ceftazidime, inhaled colistin, oral doxycycline, IV imipenem, oral trimethoprim/ sulfamethox- azole	2000 mg q8h over 3 hours (42 days)	42	Headache (physician assessed as unrelated to cefiderocol)	Reported as doing well, discharged from hospital, and completed a total of 3 weeks of cefiderocol infusions at home. Patient had no infectious complications posttransplant as of 14 March 2019.
Case 39/ Switzer- land	28 y/ Female	Postoperative wound infection with osteomyelitis after a complicated tibia fracture	Post- operative wound infection with osteo- myelitis of tibia fracture	<i>Pseudomonas aeruginosa</i> VIM, <i>Acinetobacter baumannii</i> OXA-23, <i>Enterobacter cloacae</i> KPC, and <i>Achromo- bacter xylosoxydans</i>	Cubicin, colistin, tigecycline, ceftazidime/ avibactam	2000 mg q8h (20 days)	20	None reported	Bone infection completely healed.

Patient/ Country	Age/ Gender	Relevant Medical History	Infection Type	Causative Pathogen	Concomitant Antibiotics	Cefiderocol Dose and Regimen	Duration Cefiderocol Treatment, days	Reported SAEs	Patient Outcome
Case 40/ USA	28 y/ Female	Cystic fibrosis with <i>Achromobacter</i> infection post lung transplant	Respiratory infection	<i>Achromobacter</i>	Sulfamethox- azole/ trimethoprim, colistin	1500 mg q8h over 3 hours (5 days), increased to 2000 mg q8h over 3 hours (10 days)	15	None reported	Reported as doing well, discharged home on same day stopped cefiderocol.
Case 42/ UK	16 y/ Female	Known AML, postchemo- therapy and hemopoietic transplant; developed generalized infection and sepsis	BSI	Pan-resistant <i>Pseudomonas</i> <i>aeruginosa</i> VIM metallo- beta- lactamase and ESBL <i>Escherichia</i> <i>coli</i>	Meropenem, ciprofloxacin	2000 mg q8h (6 days)	6	Death (physician assessed as unrelated to cefiderocol)	Patient died due to sepsis from disseminated herpes simplex virus and bacterial infections.
Case 43/ USA	26 y/ Female	Cystic fibrosis post lung transplant	Respiratory infection	MDR <i>Burkholderia</i> <i>cepacia</i> <i>complex</i>	Ceftazidime/ avibactam, aztreonam, posaconazole, sulfa methoxazole/ trimethoprim, azithromycin	1500 mg q8h over 3 hours (22 days)	22	None reported	Patient was discharged and reported to have improved; cervical lymphaden- opathy improved in size and symptomatic-ally during treatment.

Patient/ Country	Age/ Gender	Relevant Medical History	Infection Type	Causative Pathogen	Concomitant Antibiotics	Cefiderocol Dose and Regimen	Duration Cefiderocol Treatment, days	Reported SAEs	Patient Outcome
Case 45/ Spain	55 y/ Male	EndoTIPSitis	Prosthetic- related infection	MDR <i>Pseudomonas aeruginosa</i>	None reported	1500 mg TID (37 days)	37	None reported	Evolution regarding bacteremia was good; patient was discharged.
Case 47/ Sweden	37 y/ Male	Complicated intra-abdominal infection/ acute pancreatitis, multiple pancreatic necroses, various pseudocysts, and abdominal abscesses	cIAI	MDR <i>Acinetobacter baumannii</i>	Colistin, rifampicin	1500 mg TID (10 days)	10	Death, determined as not related to cefiderocol	Patient died due to necrosis of the pancreas and adjacent abdominal compartments with infection and multiorgan failure.
Case 48/ USA	41 y/ Male	Cystic fibrosis exacerbation with chronic bronchiectasis	Pneumonia	XDR <i>Achromo bacter denitrificans</i>	Eravacycline; azithromycin; ceftolozane/ tazobactam colistin nebulized	2000 mg IV q6h	67	None reported	Discharged to home.
Case 49/ USA	60 y/ Male	Type 2 diabetes; multiple infections; tracheostomy; acute kidney failure; severe myopathy; cardiac arrhythmias	Osteo- myelitis, myositis and polysite abscesses	<i>Pseudomonas aeruginosa</i>	Amikacin; linezolid; micafungin	0.75g q12h	58	Embolic stroke considered not related to cefiderocol or any other treatment	Discharged to a rehabilitation facility.

Patient/ Country	Age/ Gender	Relevant Medical History	Infection Type	Causative Pathogen	Concomitant Antibiotics	Cefiderocol Dose and Regimen	Duration Cefiderocol Treatment, days	Reported SAEs	Patient Outcome
Case 51/ USA	44 y/ Male	Cystic fibrosis; Respiratory tract infection; Severe hypoxia requiring intubation	Respiratory tract infection	<i>Pseudomonas aeruginosa</i> and MDR <i>P. aeruginosa</i>	Inhaled colistimethate piperacillin/ tazobactam; azithromycin	1 g q8h	22	Death; cause not specified	Patient died.
Case 53/ USA	50 y/ Male	Paraplegic due to gunshot wound	Bone/joint infection in his native hip	MDR <i>Acinetobacter baumannii</i>	Daptomycin; cefepime; polymyxin B	1g q8h (11 days) 1.5 g q8h (2 days) 2 g q8h (4 days) 1.5 g q8h (2 days) 2 g q8h (20 days)	44	None reported	Discharged to rehabilitation to complete treatment.
Case 54/ USA	46 y/ Male	Osteomyelitis in the foot (side not specified)	Intra- abdominal abscess	XRD <i>Pseudomonas aeruginosa</i> ; <i>Enterococcus faecium</i>	Metroni- dazole, linezolid	0.75 g IV q12h	27	None reported	Discharged to home.
Case 55/ USA	16 y/ Male	Cystic fibrosis, post bilateral lung transplant, diabetes mellitus, low bone density, and GJ-tube dependence	Sternal osteomye- litis, chest wall phlegmon	Pan-resistant <i>Burkholderia cepacia</i>	Azithromycin tobramycin (inhaled), minocycline voriconazole	2 g q8h	88	None reported	Discharged to home.

Patient/ Country	Age/ Gender	Relevant Medical History	Infection Type	Causative Pathogen	Concomitant Antibiotics	Cefiderocol Dose and Regimen	Duration Cefiderocol Treatment, days	Reported SAEs	Patient Outcome
Case 56/ USA	51 y/ Male	Dilated cardiomyopathy status post placement of a HeartMate II ventricular assist device	BSI	MDR <i>Pseudomonas aeruginosa</i>	Fluconazole, meropenem, tobramycin, vancomycin	2 g q8h	50	Eosinophilia	Doing well, but no status reported other than waiting for a heart transplant.
Case 57/ USA	60 y/ Male	Paraplegia following MVC; spondylodiscitis from polymicrobial spinal hardware infection	Spondylo-discitis	XDR <i>Pseudomonas aeruginosa</i>	Polymyxin B; daptomycin; meropenem	2 g q8h	50	None reported	Transferred to rehabilitation facility to complete treatment.
Case 60/ Italy	65 y/ Male	Cardiac tamponade; cardiothoracic surgery; CVVHDF	BSI and septic thrombo-phlebitis	KPC <i>Klebsiella pneumoniae</i> ; PDR <i>Acinetobacter baumannii</i>	Intravenous trimethoprim-sulfamethoxazole, colistin	1.5 g BID	16	None reported	Recovered from infection, negative blood cultures, and remained afebrile until death 17 days after treatment due to cardiological complications not related to treatment.

Patient/ Country	Age/ Gender	Relevant Medical History	Infection Type	Causative Pathogen	Concomitant Antibiotics	Cefiderocol Dose and Regimen	Duration Cefiderocol Treatment, days	Reported SAEs	Patient Outcome
Case 61/ USA	15 y/ Male	Fractured (left) femur, intramedullary pinning with chronic osteomyelitis	Osteomyelitis of femur	CR <i>Pseudomonas aeruginosa</i> ; ESBL <i>Klebsiella pneumoniae</i>	Aztreonam; polymyxin B; tigecycline	2 g TID	28	LFT elevated prior to cefiderocol treatment and remained high early, aztreonam dropped; polymyxin B status unknown	Treatment completed; LFT and kidney tests are normal.
Case 62/ Canada	62 y/ Male	Post Roux-en-Y gastric bypass surgery; ongoing anastomotic leak	Intra-abdominal sepsis	MDR <i>Pseudomonas aeruginosa</i>	Piperacillin-tazobactam, daptomycin, fluconazole, ceftazidime-avibactam	0.75 g q12h	4	Death	Multi-reparative surgeries failed to control leaky tissues and organ failure, care was withdrawn.
Case 65/ Italy	30 y/ Male	Acute, severe respiratory failure caused by H1N1 flu, Glucose-6-phosphate dehydrogenase deficiency	BSI	XDR <i>Acinetobacter baumannii</i>	Colistin failure	2 g q8h	26	None reported	Afebrile, PCT normal, discharged to rehabilitation facility.

Patient/ Country	Age/ Gender	Relevant Medical History	Infection Type	Causative Pathogen	Concomitant Antibiotics	Cefiderocol Dose and Regimen	Duration Cefiderocol Treatment, days	Reported SAEs	Patient Outcome
Case 66/ USA	58 y/ Male	Obesity, acute respiratory distress syndrome; gallstone pancreatitis; acute kidney injury, decubitus ulcer	Complicated intra- abdominal infection; pleural empyema; decubitus ulcer, blood	MDR <i>Pseudomonas aeruginosa</i> ; MDR <i>Morganella morganii</i>	Daptomycin; ceftazidime/ avibactam; polymyxin B	1 g q8h 04 Apr 2019 (5 days) 09 Apr 2019 1.5 g q8h 12 Apr 2019 (4 days)	9	None reported	Treatment completed.
Case 67/ USA	47 y/ Male	Cystic fibrosis post 2011 bilateral lung transplant; post- viral bronchiolitis; pancreatic insufficiency; gout, chronic kidney disease	Pneumonia	Pan-resistant <i>Pseudomonas aeruginosa</i> ; <i>myco- bacterial culture</i>	Ceftolozane- tazobactam; colistimethate sulfamethoxa zole- trimethoprim; vancomycin	2 g q8h	30	None reported	Doing well but not making much improvement with oxygenation.
Case 68/ Israel	38 y/ Female	Severe pulmonary arterial hypertension; respiratory decompensation	Ventilator- associated pneumonia	<i>Acinetobacter baumannii</i>	Colistin	2 g q8h	11	Death, acute shock	WBC and CRP improved, hemodynamic- ally stable, before acute shock, physician assessed death not related to cefiderocol.

Patient/ Country	Age/ Gender	Relevant Medical History	Infection Type	Causative Pathogen	Concomitant Antibiotics	Cefiderocol Dose and Regimen	Duration Cefiderocol Treatment, days	Reported SAEs	Patient Outcome
Case 70/ USA	60 y/ Female	Acute myeloid leukemia with multiple remissions, pancytopenia	Pneumonia, bacteremia	Pan-resistant <i>Elizabethkingia meningoseptica</i>	None specified	Not reported (Est. 2 g q8h; CrCl 96 mL/min))	6	Refractory sepsis resulting in death	Patient died.
Case 71/ USA	70 y/ Female	Chronic bronchiectasis	Bronchiec-tasis	<i>Achromo-bacter xylosoxidans</i> )	None specified	Not reported (CrCl = 54 mL/min)	26	Acute kidney failure thought by the treating physician to be colistin related	No growth of causative pathogens. Discharged to skilled nursing facility for physical rehabilitation.
Case 72/ USA	10 y/ Female	Cystic fibrosis, asthma, herpes simplex virus (cold sores), and pancreatic insufficiency	Cystic fibrosis exacerba-tion	Pan-resistant <i>Achromo-bacter spp</i>	Vabomere; followed by a bacteria strain specific bacteriophage	1325 mg q8h infusion over 3 hours	21	None reported	Significant clinical improvement when discharged to home.
Case 73/ Italy	18 mo/ Male	Immune deficiency from Gamma chain defect, allogeneic stem cell transplantation	BSI and pneumonia	MDR <i>Pseudomonas Aeruginosa</i>	Amikacin, high dose levofloxacin	60 mg/kg q8h	42	None reported	Complete resolution of pneumonia and sepsis.
Case 76/ USA	40 y/ Female	Cystic fibrosis/ bronchiectasis	Bronchiec-tasis	MDR <i>Pseudomonas aeruginosa</i>	Voriconazole; doxycycline; amikacin; miconazole; cefazolin	2 g q8h (10 days) 2 g q6h (11 days)	21	None reported	Discharged to home.

Patient/ Country	Age/ Gender	Relevant Medical History	Infection Type	Causative Pathogen	Concomitant Antibiotics	Cefiderocol Dose and Regimen	Duration Cefiderocol Treatment, days	Reported SAEs	Patient Outcome
Case 77/ Switzer land	62 y/ Male	Serial rib fractures with dislocation on right and left side, burst fracture of his superior endplate 7 (thoracic); COPD, developed iatrogenic lung injury due to chest tube placement followed by resection of upper lung lobes on both sides; decubitus of the heel, back, and thorax	Hospital acquired pneumonia, pleural effusion, and empyema	XDR <i>Acinetobacter baumannii</i> <i>Corynebacterium striatum</i> <i>Klebsiella pneumoniae</i>	Daptomycin; colistin; the colistin was stopped early during the last treatment session because of increasing creatinine	2 g q8h from 7 to 21 Apr 2019; 1.5 g q8h from 21 to 25 Apr 2019 2 g q8h from 25 to 30 Apr 2019; 2 g qh8 from 15 May 2019 to 30 Jun 2019	24 initially followed by 47 71 days total	Increased serum creatinine related to use of colistin	Completed rehabilitation and went home; he still needs 2 L of oxygen, the wounds looked good, he was afebrile, and the inflammatory markers were normal.
Case 78/ Australia	18 y/ Female	Recurrent pulmonary infection with a multidrug resistant strain of <i>Burkholderia cenocepacia</i> following CF lung transplant	Pneumonia, bacteremia, invasive pulmonary <i>Aspergillus</i>	MDR <i>Burkholderia cenocepacia</i> ; <i>Aspergillus</i>	Ceftazidime-avibactam, trimethoprim/sulfamethoxazole, and minocycline; voriconazole anidulafungin	2 g q8h	10	Respiratory failure, acute transplant rejection, multiorgan failure and disseminated intravascular coagulation due to sepsis	The patient died after removal of ECMO support.

Patient/ Country	Age/ Gender	Relevant Medical History	Infection Type	Causative Pathogen	Concomitant Antibiotics	Cefiderocol Dose and Regimen	Duration Cefiderocol Treatment, days	Reported SAEs	Patient Outcome
Case 79/ USA	50 y/ Female	End stage renal disease; severe aortic/mitral valve stenosis; corrective cardiovascular surgery; colectomy; tracheostomy	Multilobar pneumonia; abscesses covering her sternum	MDR <i>Pseudomonas aeruginosa</i>	Vancomycin; polymyxin B	No dose specified; CRRT because of kidney failure	10	Death	Patient withdrew care on (b) (6) and passed away; blood culture negative for <i>Pseudomonas</i> , but positive for VRE.
Case 82/ Spain	53- years/ Male	Acute myeloid leukemia	BSI	<i>Stenotrophomonas maltophilia</i>	Sulfamethoxazole/trimethoprim; tigecycline	2 g q8h	1 (only 2 doses)	Progression of AML	Patient died.
Case 83/ USA	60 y/ Female	Radical hysterectomy chronic kidney disease, chronic blood culture positive for PDR <i>B. cepacia</i>	Infected right ileac vascular graft surgically replaced	Pan-resistant <i>Burkholderia cepacia</i>	Bactrim®	1 g q8h	43	None reported	Blood cultures were negative after start of cefiderocol and remained negative after completion of treatment.

Patient/ Country	Age/ Gender	Relevant Medical History	Infection Type	Causative Pathogen	Concomitant Antibiotics	Cefiderocol Dose and Regimen	Duration Cefiderocol Treatment, days	Reported SAEs	Patient Outcome
Case 87/ USA	70 y/ Male	Type 2 diabetes chronic kidney disease, coronary artery disease with ischemic cardiomyopathy, and congestive heart failure	cUTI	MDR <i>Pseudomonas aeruginosa</i>	Aztreonam,	1 g q8h	23	Acute interstitial nephritis related to eosinophilia	Patient had been doing well on treatment and completed diagnostic procedure. Withdrawn because of adverse event post prostate procedure.
Case 88/ France	67 y/ Male	Knee prosthesis, implanted in (b) (6)	Knee implant related infection	MDR <i>Enterobacter cloacae</i>	None during cefiderocol treatment	2 g TID	73	None reported	Knee is not painful and patient remains afebrile.
Case 92/ Spain	37 y/ Female	Primary graft dysfunction after bi-lateral lung transplant due to CF, CVVHD	Bronchiec- tasis and bacteremia	<i>Ralstonia mannit- olilytica</i> ; <i>Morganella morganii</i>	None	1 g q8h	16	None reported	Patient died 16 days after completion of treatment with cefiderocol.
Case 99/ United Kingdom	84 y/ Male	Type 2 diabetes, severe atherosclerosis, stroke	Infected diabetic left foot, multi organ failure, AKI and sepsis	<i>Klebsiella pneumoniae</i> (OXA-48 and NDM)	Piperacillin/ tazobactam	1 g q8h	15	Elevated LFTs which decreased toward normal while on treatment	Patient died 17 days after discontinuation of cefiderocol and dialysis due to multiorgan failure.

Patient/ Country	Age/ Gender	Relevant Medical History	Infection Type	Causative Pathogen	Concomitant Antibiotics	Cefiderocol Dose and Regimen	Duration Cefiderocol Treatment, days	Reported SAEs	Patient Outcome
Case 100/ United Kingdom	66 y/ Female	Hypothyroidism, hypertension, bilateral knee replacements, and lower back surgery	Wound and elbow joint repair infection	<i>Acinetobacter baumannii</i> , <i>Acinetobacter nosocomialis</i>	Tigecycline	Initial dosage not reported (8 days), final dosage 1.5 g q8h (17 days)	25	Increased ALP thought by the treating physician to be related to bone damage	Discharged from hospital.
Case 101/ USA	47 y/ Female	Cystic fibrosis, lung transplant B-cell lymphoma, and rejection	Pneumonia	MDR <i>Stenotro- phomonas maltophilia</i>	Not reported	2 g q8h	21	None reported	Patient doing well, WBC normal.
Case 103/ USA	25 y/ Male	Cystic fibrosis; end stage lung disease	Bronchiec- tasis	MDR <i>Burkholderia cepacia</i> ; <i>Pseudomonas aeruginosa</i>	Ceftazidime; Bactrim®.	2 g q8h (CrCl 122 mL/min)	14	None reported	Discharged.
Case 104/ Italy	78 y/ Male	Chronic renal failure, endocarditis secondary to implanted cardiac pacemaker	BSI, endocar- ditis	MDR <i>P. aeruginosa</i>	Aztreonam Imipenem	Estimated at 0.75 g q12h	11	Mild epileptic seizure occurred which was attributed by the physician to imipenem which was then stopped without further seizures with continuing treatment	Patient was discharged from hospital with no signs of infection and normal inflammation index and PCT test.

Patient/ Country	Age/ Gender	Relevant Medical History	Infection Type	Causative Pathogen	Concomitant Antibiotics	Cefiderocol Dose and Regimen	Duration Cefiderocol Treatment, days	Reported SAEs	Patient Outcome
Case 106/ USA	19 y/ Male	Cystic fibrosis; end stage lung disease	Cystic fibrosis, exacer- bation	MDR <i>Burkholderia cepacia</i>	Azithromycin ceftazidime/ avibactam, meropenem, tobramycin inhalation	2 g q6h (CrCl = 146 mL/min)	15	None reported	Patient doing well, with stable clinical and vital signs.
Case 108/ Italy	19 y/ Female	Extensive burn over 75 % of body	BSI after body burn	MDR <i>Acinetobacter baumannii</i>	Colistin meropenem rifampin caspofungin	2 g q6h	9	Worsening (of pre-existing) anemia	Treatment completed; the worsening anemia was considered resolved at that time.
Case 111 Italy	35 y/ Female	Acute liver failure	Hospital acquired pneumonia compli- cated by septic shock	PDR <i>Acinetobacter baumannii</i> BAL; KPC <i>Klebsiella pneumoniae</i> BSI	Rifampicin	2 g TID (Cr CL = 14 mL/min)	14	None reported	Favorable clinical outcome was achieved despite demonstration of in vitro resistance.
Case 112/ Italy	55 y/ Female	Surgery for scoliosis with prostheses implant	ABSSSI; prostheses related bone infection	XDR <i>Acinetobacter baumannii</i>	None reported	2 g q8h	21	None reported	Favorable outcome achieved by 14 days of treatment and 7 more days of treatment for the bone infection.

Patient/ Country	Age/ Gender	Relevant Medical History	Infection Type	Causative Pathogen	Concomitant Antibiotics	Cefiderocol Dose and Regimen	Duration Cefiderocol Treatment, days	Reported SAEs	Patient Outcome
Case 113/ Italy	60 y/ Female	Post-traumatic paraplegia sacral-perineal and perianal pressure ulcers (stage IV)	Bone infection and cSSTI	MDR <i>Acinetobacter baumannii</i>	None reported	2 g q8h; CrCl = 150 mL/min	21	None reported	Complete recovery.
Case 115/ USA	43 y/ Male	Cystic fibrosis status post bilateral lung transplant; Patient on CVVHDF	Refractory septic shock, multiorgan failure	MDR <i>Pseudomonas aeruginosa spp</i>	Minocycline, Inhaled colistin, polymyxin B, meropenem, linezolid	2 g q8h (continuous dialysis rate 2.5L/h)	8	Death; multiorgan system failure (respiratory, renal, and hepatic)	Patient expired.

ABSSSI, acute bacterial skin and skin structure infection; ALK or ALP, alkaline phosphatase; ALT, alanine transaminase; AM, acute myeloid leukemia; AST, aspartate transaminase; BSI, blood stream infection; cIAI, complicated intra-abdominal infection; BID, twice a day; CF, cystic fibrosis; cSSTI, complicated skin and soft tissue infection; CRRT, continuous renal replacement therapy; CVVHDF, continuous veno-venous hemodiafiltration; ECMO, extracorporeal membrane oxygenation; HIV, human immunodeficiency virus; HSV-1, herpes simplex virus 1; ICU, intensive care unit; IV, intravenous; KPC, *Klebsiella pneumoniae* carbapenemase; LFT, liver function test; MDR, multi-drug resistant; MSSA, methicillin-sensitive *Staphylococcus aureus*; PCT, procalcitonin; PDR, pan drug-resistant; q6h, every 12 hours; q8h, every 8 hours; q12h, every 12 hours; SAE, serious adverse event; TID, three times a day; UK, United Kingdom; USA, United States of America; UTI, urinary tract infection; VRE, vancomycin resistant enterococcus; XDR, extensively drug-resistant.